Service Paper 1949

Vallee, Naomi N.

Epidemiology of Fluorine, Iodine, Manganese, Copper, Cobalt, Zinc, in Soils, plants animals and MAN

BOSTON UNIVERSITY

SCHOOL OF EDUCATION

A Service Paper

THE EPIDEMIOLOGY OF FLUORINE, IODINE, MANGANESE, COPPER, COBALT, ZINC, MOLYBDENUM IN SOILS, PLANTS, ANIMALS AND MAN

Submitted by

Naomi N. Vallee

(B.S. in Ed., Boston University, 1948)

In partial fulfillment of requirements for

the degree of Master of Education

June - 1949

First Reader: Dr. Leslie W. Irwin

Professor of Health and Physical Education

Second Reader: Dr. G. Laurence Rarick

Associate Professor of Education

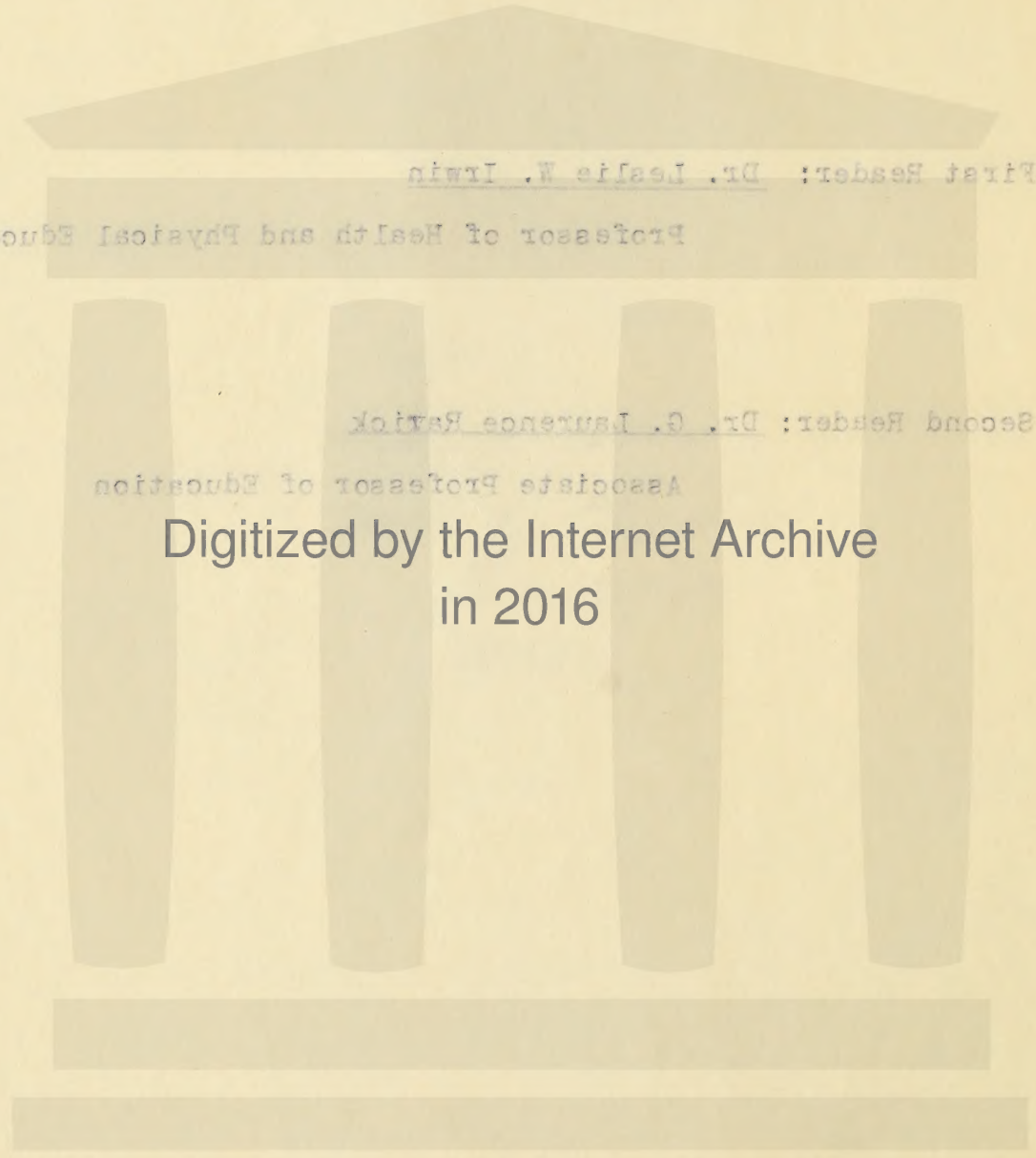


TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS (Cont'd)

TABLE OF CONTENTS (Cont'd)

Page

Chapter I

INTRODUCTION

It is perhaps justifiable when discussing the role of metals in plant, animal and human physiology to take a look at past achievements in that branch of biochemistry and compare the progress made in it with that accomplished in other major fields of body metabolism. Most textbooks of biochemistry list them as follows:

1. Carbohydrates
2. Proteins
3. Fats
4. Vitamins and Hormones
5. Minerals

It seems hardly necessary to point out that the first four have received by far the major amount of attention individually and collectively speaking. This was due in part to their relative abundance in foods and biological substrates. Progress in these fields kept pace with advances in physics, chemistry and technology allowing for inquiry into the detail of the metabolic process. These thorough studies have eventually led into concepts which no longer make such sharp delineations

Chapter I

INTRODUCTION

It is perhaps justifiable when discussing the role of metals in plant, animal and human physiology to take a look at past achievements in that branch of biochemistry and compare the progress made in it with that accomplished in other major fields of body metabolism. Most textbooks of biochemistry list them as follows:

1. Carbohydrates
2. Proteins
3. Fats
4. Vitamins and Hormones
5. Minerals

It seems hardly necessary to point out that the first four have received by far the major amount of attention individually and collectively speaking. This was due in part to their relative abundance in foods and biological substrates. Progress in these fields kept pace with advances in physics, chemistry and technology allowing for inquiry into the detail of the metabolic process. These thorough studies have eventually led into concepts which no longer make such sharp delineations

between carbohydrates, fats and proteins. Instead, one has become more and more concerned with their interconversion in the body. The role of vitamins is being explored in relation to these compounds, and enzymology has become of increasing importance because of the fundamental role which enzymes play in all these interconversions.

The body is essentially an organization of compounds of low atomic number and therefore the elements of low atomic and mass number have received a fair proportion of study. Their ions are abundant and usually collectively spoken of as "electrolytes" referring to their role in the osmotic equilibrium of the body. They exist in great preponderance -- by weight -- over the "heavy metals." This interest in the "elemental" constitution of tissues has usually found a halt at Mass Number 40 (calcium) with the notable exception of iron and iodine upon which attention was focused. The attempts at identifying the role of other heavy metals in the human body has not gone far beyond noting their presence -- if that far. Unquestionably, this fact is related to their unimpressive amounts which made quantitation difficult. As a consequence the total available literature is finite and can easily be embraced by one individual -- hardly an easy task in most biochemical

fields. At present, no adequate monograph exists on the subject of metal physiology and biochemistry. It need not be emphasized that quantity in the body as expressed by

$$R = \frac{\text{Compound under investigation}}{\text{Total body weight}}$$

is not a measure of physiological significance and importance. Vitamins, hormones and enzymes are adequate proof of this thesis. Indeed, it is lack of adequate technical tools as much as lack of interest which hampered investigations. There is no doubt that developments in physics and chemistry in the last decade have opened the avenues of approach to the role of the heavier metals in the body. While the protein, fat and carbohydrate chemists have been quick to grasp and avail themselves of new developments, there has been a considerable latent period in metal biochemistry. Therefore really very little is known concerning the occurrence and function of those elements which are found in the body in concentrations which could not be quantitated readily by conventional chemical means.

At present there is unquestionably an increased interest in this general topic which has erroneously been defined as "trace metal metabolism." The use of the word "trace" is unfortunate -- though no better one has as yet been suggested -- since "trace" implies something that

fields. At present, no adequate monograph exists on the subject of metal physiology and biochemistry. It need not be emphasized that quantity in the body as expressed by

$$R = \frac{\text{Compound under investigation}}{\text{Total body weight}}$$

is not a measure of physiological significance and importance. Vitamins, hormones and enzymes are adequate proof of this thesis. Indeed, it is lack of adequate technical tools as much as lack of interest which hampered investigations. There is no doubt that developments in physics and chemistry in the last decade have opened the avenues of approach to the role of the heavier metals in the body. While the protein, fat and carbohydrate chemists have been quick to grasp and avail themselves of new developments, there has been a considerable latent period in metal biochemistry. Therefore really very little is known concerning the occurrence and function of those elements which are found in the body in concentrations which could not be quantitated readily by conventional chemical means.

At present there is unquestionably an increased interest in this general topic which has erroneously been defined as "trace metal metabolism." The use of the word "trace" is unfortunate -- though no better one has as yet been suggested -- since "trace" implies something that

occurs in quantities so small that it can be detected qualitatively but not quantitatively. But what can or cannot be measured accurately is relative and depends entirely upon the sensitivity of the methods available which have improved greatly. The current interest has been aroused by independent advances in several fields all of which focus attention upon the hitherto unexplored elements as possible important links in the puzzle of human physiology and pathology.

Technical Considerations

Chemistry:

Work on organic dyes has revealed a considerable number which form complex salts with elements above atomic weight number 40. Many of these compounds have ideal spectrophotometric properties and allow for the identification of very small quantities of metals with very high sensitivity. These dyes are being applied to biological work with increasing frequency and success. A good example is diphenylthiocarbazone (dithizone) which may combine selectively with some ten odd metals depending on pH and the presence of complex forming salts. The combination of metals and dye manifests itself as a color change which can be measured accurately by various

occurs in quantities so small that it can be detected qualitatively but not quantitatively. But what can or cannot be measured accurately is relative and depends entirely upon the sensitivity of the methods available which have improved greatly. The current interest has been aroused by independent advances in several fields all of which focus attention upon the hitherto unexplored elements as possible important links in the puzzle of human physiology and pathology.

Technical Considerations

Chemistry:

Work on organic dyes has revealed a considerable number which form complex salts with elements above atomic weight number 40. Many of these compounds have ideal spectrophotometric properties and allow for the identification of very small quantities of metals with very high sensitivity. These dyes are being applied to biological work with increasing frequency and success. A good example is diphenylthiocarbazone (dithizone) which may combine selectively with some ten odd metals depending on pH and the presence of complex forming salts. The combination of metals and dye manifests itself as a color change which can be measured accurately by various

photoelectric means.

Physics:

(a) The advent of radioactive isotopes have made available abundant quantities of material for study. The isotopes may be added to the nutrient media of the soil, fertilizers, forage or human food intake, or they may be injected in virtually infinitesimal amounts which could hardly be detected chemically. Yet their physical radiation characteristic allow of accurate detection and will reveal information about the fashion in which these substances are handled by the body and of what importance they may be in body economy.

(b) Emission spectrography has been put to use for the trace metal physiologist. The well-known emission of light by elements on excitation in a Bunsen burner flame has long been the conventional classroom test for the identification of Na, K, Li, and other elements. This physical phenomenon, however, is a universal property of all elements and has been utilized as an extremely sensitive qualitative and quantitative tool for the detection of very small amounts of almost all elements.

Physiology:

Balance studies have occupied the major portion of the time of investigators. Such approaches have been

photoelectric means.

Physics:

(a) The advent of radioactive isotopes have made available abundant quantities of material for study. The isotopes may be added to the nutrient media of the soil, fertilizers, forage or human food intake, or they may be injected in virtually infinitesimal amounts which could hardly be detected chemically. Yet their physical radiation characteristic allow of accurate detection and will reveal information about the fashion in which these substances are handled by the body and of what importance they may be in body economy.

(b) Emission spectrography has been put to use for the trace metal physiologist. The well-known emission of light by elements on excitation in a Bunsen burner flame has long been the conventional classroom test for the identification of Na, K, Li, and other elements. This physical phenomenon, however, is a universal property of all elements and has been utilized as an extremely sensitive qualitative and quantitative tool for the detection of very small amounts of almost all elements.

Physiology:

Balance studies have occupied the major portion of the time of investigators. Such approaches have been

eminently successful in plant physiology and bacteriology. Nutrient media can easily be designed which eliminate the component under study completely. In this fashion it has been shown that deficiencies of most heavy metals either impair plant growth severely or are incompatible with life. Many strains of bacteria have thus been shown to require one or the other metal for their existence.

Deprivation studies have been much more tedious in animals or man, primarily because of the difficulty inherent in designing a metal free diet. This fact alone is adequate proof of the wide distribution of metals in foods. It is nearly impossible to free experimental diets, for carnivorous animals, of metals completely without destroying other essential components concomitantly.

Most of these experiments have aimed at the production of clinical and pathological states, hoping that they would resemble human diseases of unknown cause or throw light upon the factors controlling growth. In that sense such experiments would be very critical, indeed, if the proper techniques were available for their execution. But since this has not been possible, most animal experimentation has been concerned with intoxication rather than deprivation. Most of the work in man has been done as a result of industrial hazards and intoxication. In these instances (e.g. Zn, Cd, Be, Se)

eminently successful in plant physiology and bacteriology. Nutrient media can easily be designed which eliminate the component under study completely. In this fashion it has been shown that deficiencies of most heavy metals either impair plant growth severely or are incompatible with life. Many strains of bacteria have thus been shown to require one or the other metal for their existence.

Deprivation studies have been much more tedious in animals or man, primarily because of the difficulty inherent in designing a metal free diet. This fact alone is adequate proof of the wide distribution of metals in foods. It is nearly impossible to free experimental diets, for carnivorous animals, of metals completely without destroying other essential components concomitantly.

Most of these experiments have aimed at the production of clinical and pathological states, hoping that they would resemble human diseases of unknown cause or throw light upon the factors controlling growth. In that sense such experiments would be very critical, indeed, if the proper techniques were available for their execution. But since this has not been possible, most animal experimentation has been concerned with intoxication rather than deprivation. Most of the work in man has been done as a result of industrial hazards and intoxication. In these instances (e.g. Zn, Cd, Pb, Be)

one is often confronted with unphysiological routes of absorption which complicate an evaluation of the toxicologic effects of the metal per se. In a physiological sense these studies have added but little.

The study of interrelations of metals with other biochemical systems has nearly been limited to Fe, Cu, I, and Zn. The knowledge gained is scarcely beyond the ground stages. It may be noted in passing that the metals mentioned are all intimately concerned with respiration on the cellular level.

Epidemiology:

We have obtained a major amount of information from spontaneous occurrences of diseases in animals and plants. Some of these pathological states have been traced conclusively to the lack of one or the other or several so-called trace-metals in the food supply. The epidemiology of these investigations has been of the greatest aid in elucidating the relationship of the condition to the environment; the soil in the case of grasses, vegetables and trees; the forage in the case of animals. It should not be too surprising that the presence of deficiency states in the soil of an area results in deficiencies of plants and animals in that same area. The subsequent syndromes can easily be remedied by the

one is often confronted with unphysiological routes of absorption which complicate an evaluation of the toxicologic effects of the metal per se. In a physiological sense these studies have added but little.

The study of interrelations of metals with other biochemical systems has nearly been limited to Fe, Cu, I, and Zn. The knowledge gained is scarcely beyond the ground stages. It may be noted in passing that the metals mentioned are all intimately concerned with respiration on the cellular level.

Epidemiology:

We have obtained a major amount of information from spontaneous occurrences of diseases in animals and plants. Some of these pathological states have been traced conclusively to the lack of one or the other or several so-called trace-metals in the food supply. The epidemiology of these investigations has been of the greatest aid in elucidating the relationship of the condition to the environment; the soil in the case of grasses, vegetables and trees; the forage in the case of animals. It should not be too surprising that the presence of deficiency states in the soil of an area results in deficiencies of plants and animals in that same area.
The subsequent syndromes can easily be remedied by the

addition of the lacking element to the food intake. Minute quantities of the order of milligrams may be all that is needed.

Surprisingly enough, no concerted effort has been made to carry this type of investigation the logical step forward: to explore the effect of the metal-poor environment on man, who after all is quite as dependent upon his environment for his biochemical make-up as are the lower forms of life. The major handicap here seems to have been due to the lack of information concerning the existence of metal deficiency states in man and their possible manifestations. Yet, circumstantial evidence is abundant to make such a hypothesis eminently reasonable as will be shown.

addition of the lacking element to the food intake. Minute quantities of the order of milligrams may be all that is needed.

Surprisingly enough, no concerted effort has been made to carry this type of investigation the logical step forward: to explore the effect of the metal-poor environment on man, who after all is quite as dependent upon his environment for his biochemical make-up as are the lower forms of life. The major handicap here seems to have been due to the lack of information concerning the existence of metal deficiency states in man and their possible manifestations. Yet, circumstantial evidence is abundant to make such a hypothesis eminently reasonable as will be shown.

Chapter II

THE PROBLEM

In the case of iodine and fluorine epidemiological studies relating the environment to human physiology and pathology have successfully contributed information which has had very important consequences in the understanding and treatment of thyroid and dental abnormalities. Yet these elements are the only ones on record where such an attempt has seriously been made. The lack of enthusiasm about this approach is the more difficult to understand since it was so successful in these two instances. It is the epidemiological approach which this paper purports to stress and suggest for a critical evaluation of available data.

This discussion will present the existing information on copper, cobalt, zinc, manganese and molybdenum, elements occurring in plants and animals in minute amounts, yet being of recognized importance in their physiology and pathology. It will propose means and methods of epidemiological studies correlating their occurrence to human pathological states. As will become evident such a study will require the cooperation of various agencies and will be very time consuming, and the

Chapter II

THE PROBLEM

execution of this proposal will therefore have to be the substance of another paper. But it is hoped that this report will lay the foundation for an extended survey which may well provide the clue for the etiology of one of the human ailments, the cause of which is hitherto unknown.

execution of this proposal will therefore have to be the substance of another paper. But it is hoped that this report will lay the foundation for an extended survey which may well provide the clue for the etiology of one of the human ailments, the cause of which is hitherto unknown.

Chapter III

THE EXAMPLE

Iodine

Iodine is stored in the thyroid gland and is essential for the production of thyroglobulin and thyroxin which regulatesoxidation, the metabolic rate, controls growth, affects the autonomic nervous system and has a reciprocal relationship with other endocrine organs, particularly the pituitary.

Endemic goiter and cretinism in man and animals are the direct results of iodine deficiency in food and water intake.

The epochal discovery of Bauman (1) that the thyroid gland of mammals contains iodine laid the foundation for the isolation of the active principle some twenty years later. But it was not until 1921 that Marine and his associates proved endemic goiter to be the result of iodine deficiency in the food and water supply. Their studies led to the identification of the "Goiter Belt" of the Great Lakes area. Geologically the land of this area

---

1) Baumann, E.: Uber das normale Vorkommen von Jod im Thierkoerper; Ztshrft. Physiol. Chem. 21, 319, 1895-1896.

Chapter III

THE EXAMPLE

Iodine

Iodine is stored in the thyroid gland and is essential for the production of thyroglobulin and thyroxin which regulate oxidation, the metabolic rate, control growth, affects the autonomic nervous system and has a reciprocal relationship with other endocrine organs, particularly the pituitary.

Endemic goiter and cretinism in man and animals are the direct result of iodine deficiency in food and water intake.

The epochal discovery of Baumann (1) that the thyroid gland of mammals contains iodine laid the foundation for the isolation of the active principle some twenty years later. But it was not until 1921 that Marine and his associates proved endemic goiter to be the result of iodine deficiency in the food and water supply. Their studies led to the identification of the "Goiter Belt" of the Great Lakes area. Geologically the land of this area

---

1) Baumann, E.: Über das normale Vorkommen von Jod im Thierkörper; Ztschrft. Physiol. Chem. 21, 319, 1895-1896.

has constituted the shores of a receeding body of water which leeched out the mineral constituents and as a consequence left the soil poor in iodine and many other minerals. As a consequence vegetation, animals and man suffer from iodine deficiencies.

These realizations have necessitated large scale Public Health measures which encompass the addition of iodine to fertilizers (2,3), to the forage of cows (to increase the milk content)(4), the feed of hens (to increase the egg iodine content)(5), and most important of all the addition of iodine to the drinking water and table salt. The latter measure has been nationwide.

Fluorine

In contrast to iodine another halogen, fluorine, has never been shown to have any untoward deficiency effects. Oddly enough, an increased fluorine intake may

---

2) McHargue, J.S., Young, D.W., Calfee, R.K.: The effect of certain fertilizer materials on the iodine content of certain foods; Jour. Amer. Soc. Agron., 27, 559-565, 1935.

3) McHargue, J.S., Roy, W.R., Pelphrey, J.G.: Iodine in some fertilizer materials; Amer. Fertilizer, 73, 46-63 1930.

4) McHarg, Orasby: Iodized milk and the human diet; Milk Dealer, 24, 7, 76-80, 1935.

5) Asmundson, V.S., Almquist, H.J., Klose, A.A.: Effect of different forms of iodine on laying hens; Jour. of Nutr., 12, 1-14, 1936.

has constituted the shores of a receding body of water which leached out the mineral constituents and as a consequence left the soil poor in iodine and many other minerals. As a consequence vegetation, animals and man suffer from iodine deficiencies.

These realizations have necessitated large scale Public Health measures which encompass the addition of iodine to fertilizers (2,3), to the forage of cows (to increase the milk content)(4), the feed of hens (to increase the egg iodine content)(5), and most important of all the addition of iodine to the drinking water and table salt. The latter measure has been nationwide.

Fluorine

In contrast to iodine another halogen, fluorine, has never been shown to have any untoward deficiency effects. Oddly enough, an increased fluorine intake may

---

2) McHargue, J.S., Young, D.W., Dalton, P.K.: The effect of certain fertilizer materials on the iodine content of certain foods; Jour. Amer. Soc. Agron., 27, 589-595, 1935.

3) McHargue, J.S., Roy, W.R., Tebbutt, J.G.: Iodine in some fertilizer materials; Amer. Fertilizer, 73, 48-53 1930.

4) McHarg, Orsby: Iodized milk and the human diet; Milk Dealer, 24, 7, 76-80, 1935.

5) Asmundson, V.S., Almquist, H.J., Rose, A.A.: Effect of different forms of iodine on laying hens; Jour. of Nutr., 13, 1-14, 1936.

produce a detrimental effect (endemic fluorosis, mottled enamel) and a favorable response (prevention of dental caries).

The investigation of the effect of this element is, however, a brilliant example of the value of epidemiological studies for the investigation of the problem. Practically all of the groundwork was laid in this fashion.

It has been shown, mostly in the southwestern United States (6,7,8,9,10) that an excess of fluorine in drinking water will cause mottled enamel by affecting teeth during the period of calcification. An increase as small as 0.5 p.p.m. of water (from 1 p.p.m. to 1.5 p.p.m.) a truly infinitesimal quantity, will bring about these changes. Large scale studies have proven that a

---

6) Smith, Margaret C., Lantz, Edith M., Smith, H.V.: The cause of mottled enamel. A defect of human teeth; Arizona Agr. Expt. Sta. Tech. Bull., 32, 254-282, 1941.

7) Lantz, Edith M., Smith, H.V.: Further studies in mottled enamel; Jour. Amer. Dental Assoc., 22, 817-829, 1935.

8) Smith, Margaret C., Osborn, Foster E.: Mottled enamel in the Salt River Valley and the fluorine content of water supplies; Arizona Agr. Expt. Sta. Tech. Bull; 61, 373-418, 1936.

9) Bull, F.A.: The role of fluorine in dental health; J. Amer. Dental Assoc., 30, 1206-1215, 1943.

10) Deathrage, Charles F.: Study of fluorine containing domestic waters and dental caries experience in 263 white Illinois selective servicemen living in fluoride area following period of calcification of permanent teeth; J. Dental Research, 22, 173-180, 1943.

produce a detrimental effect (endemic fluorosis, mottled enamel) and a favorable response (prevention of dental caries).

The investigation of the effect of this element is, however, a brilliant example of the value of epidemiological studies for the investigation of the problem. Practically all of the groundwork was laid in this fashion.

It has been shown, mostly in the southwestern United States (6,7,8,9,10) that an excess of fluorine in drinking water will cause mottled enamel by affecting teeth during the period of calcification. An increase as small as 0.5 p.p.m. of water (from 1 p.p.m. to 1.5 p.p.m.) a truly infinitesimal quantity, will bring about these changes. Large scale studies have proven that a

---

6) Smith, Margaret C., Lantz, Edith M., Smith, H.V.: The cause of mottled enamel. A defect of human teeth; Arizona Agr. Expt. Sta. Tech. Bull., 32, 254-282, 1941.

7) Lantz, Edith M., Smith, H.V.: Further studies in mottled enamel; Jour. Amer. Dental Assoc., 22, 817-839, 1935.

8) Smith, Margaret C., Osborn, Foster V.: Mottled enamel in the Salt River Valley and the fluorine content of water supplies; Arizona Agr. Expt. Sta. Tech. Bull.; 81, 373-418, 1936.

9) Bull, F.A.: The role of fluorine in dental health; J. Amer. Dental Assoc., 30, 1808-1815, 1943.

10) Deatherage, Charles F.: Study of fluorine containing domestic waters and dental caries experience in 2853 white Illinois selective servicemen living in fluoride area following period of calcification of permanent teeth; J. Dental Research, 22, 173-180, 1943.

reduction of the element in the water supply will prevent or revert these effects.

There is sufficient evidence to believe that some plants absorb fluorine from the soil (11) and consequently cause fluorosis in animals who ingest them. Fluorosis of permanent incisors of cattle (12) has been known to occur in cattle grazing near brick industries.

Most of the city water supplies do not contain toxic concentrations of fluorine but there are known areas (13) in Arizona, California, Colorado, Florida, Idaho, Iowa, Kansas, Minnesota, Mississippi, Montana, Nebraska, North Dakota, South Dakota, Ohio, Oregon, Texas, Utah, Wisconsin and Wyoming -- virtually half of the United States where water contains toxic doses of fluorine and causes fluorosis in children during the period of enamel formation.

---

11) Mitchell, H.H., Edman, Marjorie: Fluorine in soils, plants and animals; Soil Science, 60, 81-90, 1945.

12) Blakemore, F.: Industrial fluorosis of animals in England; Proc. Nutr. Soc., 1, 211-215, 1944.

13) Smith, Margaret C.: Fluorine; Yearbook of Agr. U.S. Govt. Printing Office, Washington, D.C., 212-213, 1939.

reduction of the element in the water supply will prevent or revert these effects.

There is sufficient evidence to believe that some plants absorb fluorine from the soil (11) and consequently cause fluorosis in animals who ingest them. Fluorosis of permanent incisors of cattle (12) has been known to occur in cattle grazing near brick industries.

Most of the city water supplies do not contain toxic concentrations of fluorine but there are known areas (13) in Arizona, California, Colorado, Florida, Idaho, Iowa, Kansas, Minnesota, Mississippi, Montana, Nebraska, North Dakota, South Dakota, Ohio, Oregon, Texas, Utah, Wisconsin and Wyoming -- virtually half of the United States where water contains toxic doses of fluorine and causes fluorosis in children during the period of enamel formation.

---

11) Mitchell, H.H., Edman, Marjorie: Fluorine in soils, plants and animals; Soil Science, 60, 81-90, 1945.

12) Blakemore, F.: Industrial fluorosis of animals in England; Proc. Nutr. Soc., I, 211-218, 1944.

13) Smith, Margaret C.: Fluorine; Yearbook of Agr. U.S. Govt. Printing Office, Washington, D.C., 213-213, 1939.

Just to make the story more confusing Armstrong (14,15) showed that the enamel of sound teeth contained more fluorine than did carious teeth, making fluorine the only element whose concentration differs in sound and carious teeth. Numerous papers have since appeared with supporting evidence for a relationship between fluorine and the incidence of dental caries. Interestingly enough there are many epidemiological and clinical observations -- prior to Armstrong's discovery -- pointing out a decreased severity of dental caries in areas of endemic fluorosis (9,10).

The inverse relationship between incidence of dental fluorosis and dental caries has since been substantiated by the epidemiological studies of Dean and his coworkers.

These findings are a great tribute to epidemiological investigations. Unfortunately, the concomitant effect of mottling enamel makes the use of fluorine as an inhibitor of dental caries a strictly experimental procedure, though the use of topical applications offer some hope for a safe form of therapy.

---

14) Armstrong, W.D.: Fluorine content of enamel and dentin of sound and carious teeth; J.B.C., V, 119, 1937.

15) Armstrong, W.D., Berkhus, P.J.: Possible relationship between the fluorine content of enamel and resistence to dental caries; J. Dent. Res., 17, 393, 1938.

Just to make the story more confusing Armstrong (14,15) showed that the enamel of sound teeth contained more fluorine than did carious teeth, making fluorine the only element whose concentration differs in sound and carious teeth. Numerous papers have since appeared with supporting evidence for a relationship between fluorine and the incidence of dental caries. Interestingly enough there are many epidemiological and clinical observations -- prior to Armstrong's discovery -- pointing out a decreased severity of dental caries in areas of endemic fluorosis (9,10).

The inverse relationship between incidence of dental fluorosis and dental caries has since been substantiated by the epidemiological studies of Dean and his coworkers.

These findings are a great tribute to epidemiological investigations. Unfortunately, the concomitant effect of mottling enamel makes the use of fluorine as an inhibitor of dental caries a strictly experimental procedure, though the use of topical applications offer some hope for a safe form of therapy.

---

14) Armstrong, W.D.: Fluorine content of enamel and dentin of sound and carious teeth; J.D.R., V, 119, 1937.

15) Armstrong, W.D., Berkhus, P.J.: Possible relationship between the fluorine content of enamel and resistance to dental caries; J. Dent. Res., 17, 393, 1938.

Chapter IV

COPPER

The Soil and Vegetation

Two well defined diseases are now attributed to a soil copper deficiency: Exanthema or Die-Back of citrus and other fruit trees and Reclamation disease of herbaceous plants.

In 1917 Floyd (16) first observed Exanthema in citrus trees in Florida and in 1928 Smith and Thomas (17) reported a similar condition affecting other fruit trees in California. The first conclusive evidence that copper was essential for plant growth was presented by Sommer (18,19) in 1930 who demonstrated the occurrence of Exanthema in tomato, sunflower and flax plants when grown in media deficient of this element. Later in 1935 Haas and

---

16) Floyd, B.F.: Dieback or exanthema of citrus trees; Bull. Fla. Agric. Exp. Sta., No. 140, p. 1-31, 1917.

17) Smith, R.E., Thomas, H.E.: Copper sulphate as a remedy for exanthema in prunes, applies, pears and olives; Phytopathology, 18, 449-54.

18) Sommer, A.L.: Elements necessary in only small amounts for plant growth; Amer. Fert., 72, No. 6, p. 15-18, 1930.

19) Sommer, A.L.: Copper as an essential to plant growth; Plant Physiol., 6; p. 339-345, 1931.

Chapter IV

COPPER

The Soil and Vegetation

Two well defined diseases are now attributed to a soil copper deficiency: Exanthema or Die-Back of citrus and other fruit trees and Reclamation disease of herbaceous plants.

In 1917 Floyd (16) first observed Exanthema in citrus trees in Florida and in 1928 Smith and Thomas (17) reported a similar condition affecting other fruit trees in California. The first conclusive evidence that copper was essential for plant growth was presented by Sommer (18,19) in 1930 who demonstrated the occurrence of Exanthema in tomato, sunflower and flax plants when grown in media deficient of this element. Later in 1935 Haas and

---

16) Floyd, B.F.: Dieback or exanthema of citrus trees; Bull. Fla. Agric. Exp. Sta., No. 140, p. 1-31, 1917.

17) Smith, R.E., Thomas, H.E.: Copper sulphate as a remedy for exanthema in prunes, apples, pears and olives; Phytopathology, 18, 449-54.

18) Sommer, A.L.: Elements necessary in only small amounts for plant growth; Amer. Fert., 72, No. 8, p. 15-18, 1930.

19) Sommer, A.L.: Copper as an essential to plant growth; Plant Physiol., 6; p. 339-345, 1931.

Quayle (20) performed control studies on citrus trees and found that Exanthema developed only in trees grown in copper deficient soil. Exanthema is characterized by the development of chlorosis and rosetting of the leaves, the branches eventually are affected and die.

A similar state was observed in plants grown on reclaimed heath and moorland soils in Denmark, Holland and other parts of Europe (21), whence the eponym, Reclamation disease, exists.

Reclamation disease affects oats, wheat, barley and other cereals but the symptoms are identical with those of Exanthema and were attributed to a copper deficiency by Brandenberg (22) in 1933. His studies showed that exclusion of copper from the soil resulted in poor growth and plants showed symptoms of Reclamation disease. With the addition of small amounts of copper growth was more normal but fruiting was absent unless

---

20) Haas, A.R.C.; Quayle, H.J.: Copper content of citrus leaves and fruit in relation to exanthema and fumigation injury; Hilgardia, 9, p. 143-177,1935.

21) Sjollema, B.: Kupfermangel als ursache von krankheiten bei pflanzen und tieren; Biochem. Z., 267, p. 151-156, 1933.

22) Brandenburg, E.: Anderzoekingen over ontginningsziekte, II Tijdschr. Plziekt. 39, p. 189-192, 1933.

Quayle (30) performed control studies on citrus trees and found that Exanthems developed only in trees grown in copper deficient soil. Exanthema is characterized by the development of chlorosis and roasetting of the leaves, the branches eventually are affected and die.

A similar state was observed in plants grown on reclaimed heath and moorland soils in Denmark, Holland and other parts of Europe (31), whence the country, Reclamation disease exists.

Reclamation disease affects oats, wheat, barley and other cereals but the symptoms are identical with those of Exanthema and were attributed to a copper deficiency by Brandenberg (32) in 1933. His studies showed that exclusion of copper from the soil resulted in poor growth and plants showed symptoms of Reclamation disease. With the addition of small amounts of copper growth was more normal but fruiting was absent unless

---

30) Haas, A.R.C.; Quayle, H.J.: Copper content of citrus leaves and fruit in relation to exanthema and fumigation injury; Hilgardia, 8, p. 143-177,1933.

31) Sjollema, B.: Kupfermangel als ursache von Krankheiten bei pflanzen und tieren; Biochem. Z., 287, p. 151-158, 1933.

32) Brandenburg, E.: Andersuchungen over ontginning-asiekte, II Tijdschr. Plaziekt. 39, p. 189-192, 1933.

the concentration of copper was markedly increased. In 1942 Piper (23) in Australia performed similar experiments and arrived at the same conclusion. He emphasized that there are varying degrees of this deficiency, ranging from a slight decrease in yield to almost no growth.

Copper deficiency has been known to occur in plants grown on sandy and gravelly soils in Australia (24), South Africa (25) and on newly cultivated peat soils in the eastern part of the United States (26). Since Exanthema is now well known and attributed to a copper deficiency, the addition of copper salts in the form of fertilizers is a routine preventive measure in New Zealand and Australia and practiced in Holland, Denmark and the United States to varying extents.

---

23) Piper, C.S.: Investigations on copper deficiency in plants; J. Agric. Sci., 32, p. 143-178, 1942.

24) Teakle, L.J.H.: Experiments with micro-elements for the growth of crops in western Australia: VI. Further results from the use of copper-containing fertilizer in the wheat belt; Jour. Dept. Agr. West. Aust., 19, p. 242-253, 1942.

25) Anderssen, F.G.: Chlorosis in deciduous trees due to a copper deficiency; Jour. Pomol. and Hort. Sci., 10, 130-146, 1932.

26) Rademacher, B.: The state of our knowledge of the importance of copper as a trace element; Fortschr. Landw. Chem. Forsch., p. 149-160, 1937.

the concentration of copper was markedly increased.

In 1942 Piper (23) in Australia performed similar experiments and arrived at the same conclusion. He emphasized that there are varying degrees of this deficiency, ranging from a slight decrease in yield to almost no growth.

Copper deficiency has been known to occur in plants grown on sandy and gravelly soils in Australia (24), South Africa (25) and on newly cultivated peat soils in the eastern part of the United States (26). Since Exanthema is now well known and attributed to a copper deficiency, the addition of copper salts in the form of fertilizers is a routine preventive measure in New Zealand and Australia and practiced in Holland, Denmark and the United States to varying extents.

---

23) Piper, C.S.: Investigations on copper deficiency in plants; J. Agric. Sci., 32, p. 143-172, 1942.

24) Teakle, L.J.H.: Experiments with micro-elements for the growth of crops in western Australia: VI. Further results from the use of copper-containing fertilizer in the wheat belt; Jour. Dept. Agr. West. Aust., 19, p. 242-253, 1942.

25) Andersson, F.G.: Chlorosis in deciduous trees due to a copper deficiency; Jour. Pomol. and Hort. Sci., 10, 130-146, 1932.

26) Rademacher, B.: The state of our knowledge of the importance of copper as a trace element; Portschr. Landw. Chem. Forsch., p. 149-180, 1937.

Animals

In 1928 Hart, Steenbock, Waddell and Elvehjem (27) and McHargue, Healy and Hill (28) first found copper to be essential for mammalian utilization of iron in haemoglobin formation. Their studies were performed on rats and showed that copper itself does not form part of the haemoglobin molecule, but it was assumed that it had a catalytic function in its formation. These rats were fed diets deficient of copper and developed an anemia which was cured by the addition of copper salts to the diet.

In 1933 Sjollema (21) in Holland had observed a disease in cattle which was characterized by an anemia, loss of appetite and general degeneration. This disease occurred in the same area where he had observed Reclamation disease affecting cereal plants. An analysis of the hay showed a deficiency of copper and when copper was added to the diet the condition improved. Recovery also occurred when the animals were moved to areas where Reclamation disease in plants was absent. He called this disease

---

27) Hart, E.B., Steenbock, H., Waddell, J., Elvehjem, C.A.: Iron in nutrition. VII. Copper as a supplement to iron for haemoglobin building in the rat; J. Biol. Chem., 77, 797-812, 1928.

28) McHargue, J.S., Healy, D.J., Hill, E.S.: The relation of copper to the hemoglobin content of rat blood; J. Biol. Chem., 78, 637-641, 1928.

Animals

In 1929 Hart, Steenbock, Waddell and Elvehjem (27) and McHargue, Healy and Hill (28) first found copper to be essential for mammalian utilization of iron in haemoglobin formation. Their studies were performed on rats and showed that copper itself does not form part of the haemoglobin molecule, but it was assumed that it had a catalytic function in its formation. These rats were fed diets deficient of copper and developed an anemia which was cured by the addition of copper salts to the diet.

In 1933 Sjollema (21) in Holland had observed a disease in cattle which was characterized by an anemia, loss of appetite and general degeneration. This disease occurred in the same area where he had observed Peclamation disease affecting cereal plants. An analysis of the hay showed a deficiency of copper and when copper was added to the diet the condition improved. Recovery also occurred when the animals were moved to areas where Peclamation disease in plants was absent. He called this disease

---

27) Hart, E.B., Steenbock, H., Waddell, J.; Elvehjem, C.A.: Iron in nutrition. VII. Copper as a supplement to iron for haemoglobin building in the rat; J. Biol. Chem., 77, 797-812, 1928.

28) McHargue, J.S., Healy, D.J., Hill, E.S.: The relation of copper to the haemoglobin content of rat blood; J. Biol. Chem., 78, 637-641, 1928.

"Licking disease" for these animals had Anorexia and a selective craving for copper licks when these were made available in the form of copper salts.

A similar disease of cattle called "Salt Sick" was observed in Florida (29) in 1931 and was cured by the addition of copper salts to the diet. It is probably identical with Licking disease.

A disease of lambs attributed to a shortage of copper has been known to occur in various parts of Great Britain in the areas of Derbyshire, Yorkshire and Gloucestershire and was first described by Stewart in 1932 (30). The disease is known as Swayback, or Swingback and in Australia a similar disease was known as Enzootic Ataxia, described by Bennets (31) in 1932. In 1939, Dunlop (32) studied Swayback in lambs. He described the symptoms as (1) incoordination of movement

---

29) Becker, R.B., Neal, W.M., Shealy, A.L.: I. Salt sick: its cause and prevention. II. Mineral supplements for cattle; Bull. Fla. Agric. Exp. Sta., No.231, p. 1-22, 1931.

30) Stewart, W.L.; Swingback (Ataxia) in lambs; Vet. J., 88, p. 133-137, 1932.

31) Bennets, H.W.: Enzoatis ataxia of lambs in western Australia; Aust. Vet. J., 8, p. 137-142; 183-184, 1932.

32) Dunlop, G., Innes, J.R.M., Shearer, G.D., and Wells, H.: "Swayback" studies in North Derbyshire. I. The feeding of copper to pregnant ewes in the control of 'Swayback", J. Comp. Path., 52, p. 259-265, 1939.

"licking disease" for these animals had Anorexia and a selective craving for copper licks when these were made available in the form of copper salts.

A similar disease of cattle called "Salt Sick" was observed in Florida (29) in 1931 and was cured by the addition of copper salts to the diet. It is probably identical with licking disease.

A disease of lambs attributed to a shortage of copper has been known to occur in various parts of Great Britain in the areas of Derbyshire, Yorkshire and Gloucestershire and was first described by Stewart in 1932 (30). The disease is known as Swayback, or Swingback and in Australia a similar disease was known as Enzootic Ataxia, described by Bennets (31) in 1932. In 1939, Dunlop (32) studied Swayback in lambs. He described the symptoms as (1) incoordination of movement

---

29) Becker, R.B., Neal, W.M., Shealy, A.L.: I. Salt sick: its cause and prevention. II. Mineral supplements for cattle; Bull. Fla. Agric. Exp. Sta., No.231, p. 1-32, 1931.

30) Stewart, W.L.: Swingback (Ataxia) in lambs; Vet. J., 88, p. 132-137, 1932.

31) Bennets, H.W.: Enzootic ataxia of lambs in western Australia; Aust. Vet. J., 8, p. 137-142; 183-194, 1932.

32) Dunlop, G., Innes, J.R.M., Shearer, G.D., and Wells, H.: "Swayback" studies in North Derbyshire. I. The feeding of copper to pregnant ewes in the control of 'Swayback". J. Comp. Path., 52, p. 256-286, 1939.

(2) swaying gait

(3) staggering

(4) collapse

(5) death

The mortality of the disease is 100% due to marked brain and cerebral cord damage. It is not inherited and when pregnant ewes are fed a diet containing sufficient copper the newborn do not have symptoms of Swayback. Dunlop's control experiments clarified the etiological relationship of this disease to copper deficiency. He distributed 1800 ewes over fifty farms. Copper salt licks were made available to half of this group and after five months all the licks were consumed. The lambs born from ewes to whom copper was available did not show any symptoms while those born of stock lacking it were seriously affected. Repeated studies by Dunlop (33) showed conclusively that Swayback in lambs can be prevented by supplying copper salts to the diet of pregnant ewes.

In 1929 Elvehjem and Hart (34) analyzed forage and found that the copper content of crops can be

---

33) Dunlop, G., Wells, H.E.: "Warfa" (Swayback) in lambs in North Derbyshire and its prevention by adding copper supplements to the diet of the ewes during gestation; Vet. Rec., 50, 1175-1182, 1938.

34) Elvehjem, C.A., Hart, E.B.: The copper content of feeding stuffs; J. Biol. Chem., Vol. LXXXII, No. 2, p. 473-477, 1929.

(2) swaying gait

(3) staggering

(4) collapse

(5) death

The mortality of the disease is 100% due to marked brain and cerebral cord damage. It is not inherited and when pregnant ewes are fed a diet containing sufficient copper the newborn do not have symptoms of Swayback. Dunlop's control experiments clarified the etiological relationship of this disease to copper deficiency. He distributed 1800 ewes over fifty farms. Copper salt licks were made available to half of this group and after five months all the licks were consumed. The lambs born from ewes to whom copper was available did not show any symptoms while those born of stock licking it were seriously affected. Repeated studies by Dunlop (33) showed conclusively that Swayback in lambs can be prevented by supplying copper salts to the diet of pregnant ewes.

In 1929 Elvehjem and Hart (34) analyzed forage and found that the copper content of crops can be

---

33) Dunlop, G., Weills, H.E.: "Marle" (Swayback) in lambs in North Derbyshire and its prevention by adding copper supplements to the diet of the ewes during gestation: Vet. Rec., 50, 1178-1182, 1938.

34) Elvehjem, C.A., Hart, E.B.: The copper content of feeding stuffs; J. Biol. Chem., Vol. LXXXII, No. 2, p. 473-477, 1929.

increased by fertilizing the soil with a copper salt and thus providing adequate amounts of copper to the diet of animals.

Man

No deficiency diseases have been demonstrated in man. However Elvehjem and Hart (27) in 1928 have established the fact that copper is present in human blood and aids in the utilization of iron for the formation of haemoglobin. Extension of this work in 1931 (35) and 1937 (36) by others have shown that infants suffering from a nutritional anemia had a more rapid increase in haemoglobin formation when treated with copper and iron as compared with those treated with iron alone.

The isolation of a copper protein, haemocuprein, by Keilin and Mann (37) from human erythrocytes is yet another step forward, though its presence is unexplained.

---

35) Josephs, H.: Treatment of anemia of infancy with iron and copper; Bull. Johns Hopkins Hosp., 49, 246-258, 1931.

36) Elvehjem, C.A., Duckles, D., Mendenhall, Dorothy R.: Iron versus iron and copper in the treatment of anemia in infants; Amer. Jour. Diseases Children, 53, 785-793, 1937.

37) Mann, T., Keilin, D.: Haemocuprein and hepatocuprein, copper-protein compounds of blood and liver in mammals; Proc. Roy. Soc., B. 126, 303-315, 1938.

increased by fertilizing the soil with a copper salt and thus providing adequate amounts of copper to the diet of animals.

Man

No deficiency diseases have been demonstrated in man. However Elvehjem and Hart (37) in 1932 have established the fact that copper is present in human blood and aids in the utilization of iron for the formation of haemoglobin. Extension of this work in 1931 (35) and 1932 (36) by others have shown that infants suffering from a nutritional anemia had a more rapid increase in haemoglobin formation when treated with copper and iron as compared with those treated with iron alone.

The isolation of a copper protein, haemocuprein, by Keilin and Mann (37) from human erythrocytes is yet another step forward, though its presence is unexplained.

---

35) Josephs, H.: Treatment of anemia of infancy with iron and copper; Bull. Johns Hopkins Hosp., 49, 248-258, 1931.

36) Elvehjem, C.A., Duckles, D., Mendenhall, Dorothy R.: Iron versus iron and copper in the treatment of anemia in infants; Amer. Jour. Diseases Children, 53, 795-793, 1937.

37) Mann, T., Keilin, D.: Haemocuprein and hepatocuprein, copper-protein compounds of blood and liver in mammals; Proc. Roy. Soc., B. 126, 303-315, 1939.

Hypothetical Remarks

The resemblance of the clinical symptoms of Swayback to various human neurological conditions is striking (Multiple Sclerosis, Syringomyelia). No serious attempt has been made to date to examine the possible epidemiological relationship between copper available in the food and the incidence of these pathological states. This relationship might be of utmost importance.

Hypothetical Remarks

The resemblance of the clinical symptoms of Swayback to various human neurological conditions is striking (Multiple Sclerosis, Syringomyelia). No serious attempt has been made to date to examine the possible epidemiological relationship between copper available in the food and the incidence of these pathological states. This relationship might be of utmost importance.

Table I

THE EPIDEMIOLOGY OF COPPER

Deficient Areas	Plant Diseases Exanthema, Die-Back Reclamation Disease	Animal Diseases Salt Sick, Swayback, Licking Disease, Enzootic Ataxia
California	pears, prune, apricot, apple.	
Florida	garden vegetables, citrus fruits, tung.	cattle
Indiana	sugar beets, garden vegetables	cattle
New York	onions	
North Carolina	garden vegetables	
Washington	pears	
Australia	apricot citrus fruits,plum, peach	cattle lambs
Denmark	legumes oats,wheat,barley,beets	cattle
Great Britain		cattle lambs
Holland	beets, legumes	cattle
New Zealand	citrus fruits, legumes	cattle
South Africa	apple, peach, plum, apricot.	
South America		cattle

Table I

THE EPIDEMIOLOGY OF COPPER

Deficient Areas	Plant Diseases Exanthema, Die-back Reclamation Diseases	Animal Diseases Salt Sick, Swayback, Licking Diseases, Enzootic Ataxia
California	pears, prune, apricot, apple.	
Florida	Reclaimed vegetables, citrus fruits, tung.	cattle
Indiana	sugar beets, garden vegetables	cattle
New York	onions	
North Carolina	garden vegetables	
Washington	pears	
Australia	apricot citrus fruits, plum, peach	cattle lambs
Denmark	legumes oats, wheat, barley, beets	cattle
Great Britain		cattle lambs
Holland	beets, legumes	cattle
New Zealand	citrus fruits, legumes	cattle
South Africa	apple, peach, plum, apri-cot.	
South America		cattle

Chapter V

COBALT

The Soil and Vegetation

Cobalt occurs in many plants (38). The exact quantities necessary for growth are unknown. No cobalt deficiency syndromes of plants have ever been reported and it might therefore not be necessary for plant growth. Yet it is a serious fact that cattle and sheep feeding on cobalt deficient pastures show marked deficiency states.

Animals

The deficiency of this element in animals results from low soil cobalt, therefore low plant and fodder cobalt. Pine or Pining, now recognized as a cobalt deficiency disease affecting young cattle was described in Scotland in 1831 by Hogg (39) and later by Grieg and coworkers (40) in 1933. In young animals the disease is characterized

---

38) Hurwitz, Charles, Beeson, Kenneth C.: Cobalt contents of some food plants; Food Research, 9, 348-357, 1944.

39) Hogg, J.: Remarks on certain diseases of sheep; Quart. J. Agric., 2, 697-706, 1831.

40) Greig, J.R., Dryene, H., Godden, W., Crichton, A., Ogg, W.G.: Pine: a disease affecting sheep and young cattle; Vet. J., 89, 99-110, 1933.

Chapter V

COBALT

The Soil and Vegetation

Cobalt occurs in many plants (38). The exact quantities necessary for growth are unknown. No cobalt deficiency syndromes of plants have ever been reported and it might therefore not be necessary for plant growth. Yet it is a serious fact that cattle and sheep feeding on cobalt deficient pastures show marked deficiency states.

Animals

The deficiency of this element in animals results from low soil cobalt, therefore low plant and fodder cobalt. Pine or Pining, now recognized as a cobalt deficiency disease affecting young cattle was described in Scotland in 1831 by Hogg (39) and later by Grieg and coworkers (40) in 1933. In young animals the disease is characterized

---

38) Hurwitz, Charles, Beeson, Kenneth C.: Cobalt contents of some food plants; Food Research, 9, 348-357, 1944.

39) Hogg, J.: Remarks on certain diseases of sheep: Quart. J. Agric., 2, 697-708, 1831.

40) Greig, J.R., Dryerre, H., Godden, W., Crichton, A., Ogg, W.G.: Pine: a disease affecting sheep and young cattle; Vet. J., 89, 99-110, 1933.

by a retardation of growth and a stilted gait. Older animals show similar symptoms and a marked anemia. Finally the animals die as a result of extreme inanition. Similar diseases have been observed in North Ireland, New Zealand (41) where it is known as Buch Sickness and in Southland, New Zealand (42) where it is known as Morton Mains disease and in Australia (43) where it is known as Enzoatic Marasmus.

Soil analyses by spectrography in New Zealand (41) revealed that Morton Mains disease occurred in cobalt deficient areas. In 1935 Underwood and Filmer (43) treated Enzoatic Marasmus in sheep by administering cobalt nitrate and affected a complete cure. Two years later these same investigators (44) similarly cured affected cattle. In 1938 Underwood and Harvey (45) found that both soil and

---

41) Asken, H.D., Dixon, J.K.: The importance of cobalt in the treatment of certain stock ailments in the South Island, New Zealand; New Zealand J. Sc. Technol., 18, 73-84, 1936.

42) Wunsh, D.S.: Tracking down a deficiency disease; Chem. and Ind., 15, 855-859,1937.

43) Underwood, E.J., Filmer, J.F.: Enzootic Marasmus. The determination of the biologically potent element cobalt in limonite; Australian Vet. J., 11,84-92,1935.

44) Filmer, J.F., Underwood, E.J.: Enzootic Marasmus. Further data concerning the potency of cobalt as a curative and prophylactic agent; Aust. Vet. J.,13, 57-64, 1937.

45) Underwood, E.J., Harvey, R.J.: Enzootic Marasmus. The cobalt content of soils, pastures and animal organs; Aust. Vet. J., 14, 183-189, 1938.

by a retardation of growth and a stilted gait. Older animals show similar symptoms and a marked anemia. Finally the animals die as a result of extreme inanition. Similar diseases have been observed in North Ireland, New Zealand (41) where it is known as Bush Sickness and in Southland, New Zealand (42) where it is known as Morton Mains disease and in Australia (43) where it is known as Enzootic Marasmus.

Soil analyses by spectrography in New Zealand (41) revealed that Morton Mains disease occurred in cobalt deficient areas. In 1935 Underwood and Filmer (43) treated Enzootic Marasmus in sheep by administering cobalt nitrate and effected a complete cure. Two years later these same investigators (44) similarly cured effected cattle. In 1938 Underwood and Harvey (45) found that both soil and

---

41) Askew, H.D., Dixon, J.K.: The importance of cobalt in the treatment of certain stock ailments in the South Island, New Zealand; New Zealand J. Sc. Technol., 18, 73-84, 1936.

42) Wunah, D.S.: Tracking down a deficiency disease; Chem. and Ind., 15, 856-859,1937.

43) Underwood, E.J., Filmer, J.F.: Enzootic Marasmus. The determination of the biologically potent element cobalt in limonite; Australian Vet. J., 11,84-93,1935.

44) Filmer, J.F., Underwood, E.J.: Enzootic Marasmus. Further data concerning the potency of cobalt as a curative and prophylactic agent; Aust. Vet. J.,13, 57-64, 1937.

45) Underwood, E.J., Harvey, R.J.: Enzootic Marasmus. The cobalt content of soils, pastures and animal organs; Aust. Vet. J., 14, 183-189, 1938.

herbage (in areas where the disease was present) had a lower cobalt content than healthy areas. They also showed that the cobalt content of herbage could be increased by treatment of the soil with cobalt acetate. In 1938 and 1939 similar results were reported by Kidson and Maunsell (46) in New Zealand and Comer and Smith (47) in Scotland. In 1941 Stewart, Mitchell and Stewart (48) performed studies in lambs which were raised in cobalt deficient areas. Cobalt was supplemented to the diet of 40 lambs and 25 served as the control group. After ten weeks of observation, the treated animals were in good condition and continued to grow, while the control animals developed severe symptoms of Pining and eventually died. These same investigators demonstrated the effect of cobalt fertilization on the soil and herbage. They found that lambs grown on fertilized herbage continued to grow and develop normally, but lambs grown on untreated soil developed Pining.

---

46) Kidson, E.B., Maunsell, P.W.: The effect of cobalt compounds on the cobalt content of supplementary fodder crops; N.Z. J. Sci. Tech., 21A, 125-128,1939.

47) Comer, H.H., Smith, A.M.: The influence of cobalt on pine disease in sheep; Biochem. J., 32, 1800-1805, 1938.

48) Stewart, J., Mitchell, R.L., Stewart, A.B.: Pining in sheep; its control by administration of cobalt and by use of cobalt-rich fertilizers; Empire J. Exp. Agric., 9, 145-52, 1941.

herbage (in areas where the disease was present) had a lower cobalt content than healthy areas. They also showed that the cobalt content of herbage could be increased by treatment of the soil with cobalt acetate. In 1938 and 1939 similar results were reported by Kidson and Mansell (46) in New Zealand and Comer and Smith (47) in Scotland. In 1941 Stewart, Mitchell and Stewart (48) performed studies in lambs which were raised in cobalt deficient areas. Cobalt was supplemented to the diet of 40 lambs and 25 served as the control group. After ten weeks of observation, the treated animals were in good condition and continued to grow, while the control animals developed severe symptoms of pining and eventually died. These same investigators demonstrated the effect of cobalt fertilization on the soil and herbage. They found that lambs grown on fertilized herbage continued to grow and develop normally, but lambs grown on untreated soil developed pining.

---

46) Kidson, E.B., Mansell, P.W.: The effect of cobalt compounds on the cobalt content of supplementary fodder crops; N.Z. J. Sci. Tech., 21A, 125-129, 1939.

47) Comer, H.H., Smith, A.M.: The influence of cobalt on pine disease in sheep; Biochem. J., 32, 1800-1805, 1938.

48) Stewart, J., Mitchell, K.J., Stewart, A.B.: Pining in sheep; its control by administration of cobalt and by use of cobalt-rich fertilizers; Empire J. Exp. Agric., 9, 145-52, 1941.

Pine disease has been known to occur in Canada (49,50) and areas in Michigan (51), Massachusetts (52), New Hampshire (53,54), and other areas in the United States (55). Cobalt deficiency of animals may be associated with an iron and copper deficiency. It has occurred sporadically in areas where Enzoatic Ataxia was endemic and copper would cure the condition as has been discussed previously.

---

49) Bowstead, J.E., Sackville, J.P.: Studies with a deficient ration for sheep. I. Effect of various supplements. II. Effect of a cobalt supplement; Canad. Jour. Res., 17, 15-28, 1939.

50) McIntosh, R.A.: Cobalt deficiency; Canad. Jour. Compar. Med. and Vet. Sci., 9, 179-182, 1945.

51) Baltzer, A.C., Killham, B.J., Duncan, C.W., Hoffman, C. F.: A cobalt deficiency disease observed in some Michigan dairy cattle; Mich. Agr. Expt. Sta. Quart. Bull., 24, 68-70, 1941.

52) Archibald, J.G., Bennett, E.: Chemical composition of herbage from Mass. pastures; Mass. Agr. Expt. Sta. Bull; 300, 1-7, 1933.

53) Keener, H.A., Percival, G.P., Morrow, K.S.: Cobalt treatment of a nutritional disease in New Hampshire dairy cattle; New Hampshire Sta. Cir. 68, 1-8, 1944.

54) Lyford, W.H., Jr., Percival, G. P., Keener, H.A., Morrow, K.S.: The soils of N.H. as related to a deficiency in cattle responding to cobalt; Soil Sci. Am. Proc., 10, 375-380, 1945.

55) Beeson, Kenneth C., Gray, Louise, Smith, Sedgwick, E: Some areas in eastern U.S. associated with deficiencies of cobalt and other elements in the soil; Soil Sci. Am. Proc., 9, 164-168, 1944.

Pine disease has been known to occur in Canada (48,50) and areas in Michigan (51), Massachusetts (52), New Hampshire (53,54), and other areas in the United States (55). Cobalt deficiency of animals may be associated with an iron and copper deficiency. It has occurred sporadically in areas where Enzootic Ataxia was endemic and copper would cure the condition as has been discussed previously.

---

48) Bowstead, J.E., Scokville, J.P.: Studies with a deficient ration for sheep. I. Effect of various supplements. II. Effect of a cobalt supplement: Canad. Jour. Res., 17, 18-36, 1939.

50) McIntosh, R.A.: Cobalt deficiency; Canad. Jour. Compar. Med. and Vet. Sci., 9, 179-182, 1945.

51) Baltzer, A.C., Killham, R.J., Duncan, C.W., Hoffman, C. F.: A cobalt deficiency disease observed in some Michigan dairy cattle; Mich. Agr. Expt. Sta. Quart. Bull., 24, 88-70, 1941.

52) Archibald, J.G., Bennett, E.: Chemical composition of herbage from Mass. pastures; Mass. Agr. Expt. Sta. Bull; 300, 1-7, 1933.

53) Keener, H.A., Percival, G.P., Morrow, K.S.: Cobalt treatment of a nutritional disease in New Hampshire dairy cattle; New Hampshire Sta. Cir. 88, 1-8, 1944.

54) Lyford, W.H., Jr., Percival, G. P., Keener, H.A., Morrow, K.S.: The soils of N.H. as related to a deficiency in cattle responding to cobalt; Soil Sci. Am. Proc., 10, 375-380, 1945.

55) Beeson, Kenneth C., Gray, Louise, Smith, Sedgwick, E: Some areas in eastern U.S. associated with deficiencies of cobalt and other elements in the soil; Soil Sci. Am. Proc., 9, 184-188, 1944.

There is both a qualitative and quantitative difference in the fashion in which different species utilize cobalt. Horses will remain healthy on cobalt deficient pastures, while cattle and sheep will be affected.

Man

Though the studies on cobalt Polycythemia are not directly related to the subject under discussion, it is of interest to point out that by administration of cobalt a marked increase in erythrocytes (Polycythemia) has been produced in numerous species (56,57,58). It has not been possible to date to trace human Polycythemia sera to cobalt metabolism, though such studies would be of extreme interest.

In a similar vein one should recall the recent discovery of Vitamin B_{12} - seemingly the anti-pernicious principle. It is reported to contain a constant percentage

---

56) Stare, F. J., Elvehjem, C.A.: Cobalt in animal nutrition; J. Biol. Chem., 99, 473-483, 1933.

57) Waltner, Klara, Waltner, K.: Kobalt und Blut, Klin; Wchnschr., 8, 313, 1929.

58) Orten, J.M., Underhill, F.A., Mugrage, E.R., Lewis, R.C.: Polycythemia in the rat on a milk-iron-copper diet supplemented by cobalt; J. Biol. Chem., 96, 11-16, 1932.

There is both a qualitative and quantitative difference in the fashion in which different species utilize cobalt. Horses will remain healthy on cobalt deficient pastures, while cattle and sheep will be affected.

Man

Though the studies on cobalt Polycythemia are not directly related to the subject under discussion, it is of interest to point out that by administration of cobalt a marked increase in erythrocytes (Polycythemia) has been produced in numerous species (56,57,58). It has not been possible to date to trace human Polycythemia sera to cobalt metabolism, though such studies would be of extreme interest.

In a similar vein one should recall the recent discovery of Vitamin B_{12} - seemingly the anti-pernicious principle. It is reported to contain a constant percentage

---

56) Stare, F. J., Elvehjem, C.A.: Cobalt in animal nutrition; J. Biol. Chem., 99, 473-483, 1933.

57) Waltner, Klara, Waltner, K.: Kobalt und Blut, Klin; Wchnschr., 8, 313, 1929.

58) Orten, J.M., Underhill, F.A., Mugrage, E.F., Lewis, R.C.: Polycythemia in the rat on a milk-iron-copper diet supplemented by cobalt; J. Biol. Chem., 98, 11-18, 1932.

of cobalt as an integral part of the molecule (59), thus giving another lead to the tie-up of human metabolism with metal intake.

---

59) Rickes, E.L., Brink, N.G., Koniuszy, F.R., Wood, T.R., Folkers, K.: Vitamin B_{12}, a cobalt containing complex; Science, 108, 134, 1948.

of cobalt as an integral part of the molecule (59),
thus giving another lead to the tie-up of human metab-
olism with metal intake.

---

59) Rickes, E.L., Brink, N.G., Koniuszy, F.R., Wood, T.R., Folkers, K.: Vitamin B_{12}, a cobalt containing complex; Science, 108, 134, 1948.

Table II

THE EPIDEMIOLOGY OF COBALT

Deficient Areas	Plants	Animal Diseases
	No pathological manifestations have been described.	Pining, Bush sickness, Enzoatic Marasmus
	Deficiencies produce disease in animals:	Morton Mains
Florida	hay, clover	cattle
Massachusetts	corn, hay, rye grasses	dairy cattle
Michigan	alfalfa	dairy cattle
New Hampshire	corn, hay	dairy cattle
Wisconsin	alfalfa, corn, wheatgrass	cattle
Australia	"Herbage" (species not specified)	cattle
Canada	" "	cattle
New Zealand	" "	cattle
Scotland	" "	cattle

Table II

THE EPIDEMIOLOGY OF COBALT

Deficient Areas	Plants No pathological manifestations have been described. Deficiencies produce disease in animals:	Animal Diseases Pining, Bush sickness, Enzootic Marasmus Wasting Disease
Florida	hay, clover	cattle
Massachusetts	corn, hay, rye grasses	dairy cattle
Michigan	alfalfa	dairy cattle
New Hampshire	corn, hay	dairy cattle
Wisconsin	alfalfa, corn, wheatgrass	cattle
Australia	"Herbage"(species not specified)	cattle
Canada	"	cattle
New Zealand	"	cattle
Scotland	"	cattle

Chapter VI

MANGANESE

The Soil and Vegetation

It was as early as 1897 that Bertrand (60) first discovered the presence of manganese in plants and showed that it was essential for the action of laccase, an oxidizing enzyme. In 1912 McHargue (61) reported findings on the occurrence and distribution of manganese in various seeds. But it was not until 1928-1929 that diseases in plants were attributed to a manganese deficiency in the soil. At this time Samuel and Piper (62, 63) grew Algerian oats in carefully controlled cultures and found that plants grown in manganese free cultures developed a condition which they labelled "Grey Speck of

---

60) Bertrand, G.: Sur l'intervention du manganese dans les oxidations provoquees par la laccase; C. R. Acad. Sci. Paris, 124, 1032-1035, 1355-1358, 1897.

61) McHargue, J.S.: The occurrence and significance of manganese in the seed coat of various seeds; Jour. Amer. Chem. Soc., 36, 2532-2536, 1914.

62) Samuel, G., Piper, C.S.: Grey Speck (manganese deficiency) diseases of oats; J. Agric. S. Aust., 31, 696-705, 789-799, 1928.

63) Samuel, G., Piper, C.S.: Manganese as an essential element for plant growth; Ann. Appl. Biol., 16, 493-524, 1929.

Chapter VI

MANGANESE

The Soil and Vegetation

It was as early as 1897 that Bertrand (80) first discovered the presence of manganese in plants and showed that it was essential for the action of laccase, an oxidizing enzyme. In 1912 McHargue (81) reported findings on the occurrence and distribution of manganese in various seeds. But it was not until 1928-1929 that diseases in plants were attributed to a manganese deficiency in the soil. At this time Samuel and Piper (82, 83) grew Algerian oats in carefully controlled cultures and found that plants grown in manganese free cultures developed a condition which they labelled "Grey Speck of

---

80) Bertrand, G.: Sur l'intervention du manganese dans les oxidations provoquees par la laccase; C. R. Acad. Sci. Paris, 124, 1032-1035, 1355-1358, 1897.

81) McHargue, J.S.: The occurrence and significance of manganese in the seed coat of various seeds; Jour. Amer. Chem. Soc., 36, 2532-2536, 1914.

82) Samuel, G., Piper, C.S.: Grey Speck (manganese deficiency) diseases of oats; J. Agric. S. Aust., 31, 896-705, 799-799, 1928.

83) Samuel, G., Piper, C.S.: Manganese as an essential element for plant growth; Ann. Appl. Biol., 16, 495-524, 1929.

Oats." Control cultures showed no symptoms. Their studies also showed that Grey Speck can be cured by the addition of manganese salts to the culture, but that it will recur if this treatment is discontinued. The symptoms of "Grey Speck of Oats" are:

(1) Chlorosis of the leaves - appearance of grey spots.

(2) Development of a withering line and weakness across the leaf blade - the leaves fail to develop and fall.

(3) The root development is poor, the plant fails to flower and finally dies.

In 1932, Pettinger, Henderson and Wingard (64) observed symptoms -- similar to Grey Speck -- in maize and in 1943, Gallagher and Walsh (65) reported Grey Speck in wheat, barley and rye.

Another disease, similar to Grey Speck, affecting sugar cane was first observed in Pahala, Hawaii. It was not until 1928 that McHargue and Lee (66) produced evidence that this disease, Pahala Blight of Sugar Cane, results from a manganese deficiency. Their conclusions

---

64) Pettinger, N.A., Henderson, R.G., Wingard, A.: Some nutritional disorders in corn grown in sand cultures; Phytopathology, 22, 33-51, 1932.

65) Gallagher, P.H., Walsh, T.: The susceptibility of cereal rarities to manganese deficiency; J. Agric. Sci., 33, 197-203, 1943.

66) McHargue, J.S., Lee, H.A.: The effect of manganese deficiency on the sugar cane plant and its relationship to phala blight of sugar cane; Phytopath., 18, 775-786, 1928.

Oats." Control cultures showed no symptoms. Their

studies also showed that Grey Speck can be cured by

the addition of manganese salts to the culture, but

that it will recur if this treatment is discontinued.

The symptoms of "Grey Speck of Oats" are:

(1) Chlorosis of the leaves - appearance of grey spots.

(2) Development of a withering line and weakness across the leaf blade - the leaves fail to develop and fail.

(3) The root development is poor, the plant fails to flower and finally dies.

In 1932, Pettinger, Henderson and Wingard (64) observed symptoms -- similar to Grey Speck -- in maize and in 1943, Gallagher and Walsh (65) reported Grey Speck in wheat, barley and rye.

Another disease, similar to Grey Speck, affecting sugar cane was first observed in Fabala, Hawaii. It was not until 1928 that McHargue and Lee (66) produced evidence that this disease, Fabala Blight of Sugar Cane, results from a manganese deficiency. Their conclusions

---

64) Pettinger, N.A., Henderson, R.G., Wingard, A.: Some nutritional disorders in corn grown in sand cultures; Phytopathology, 22. 33-51, 1932.

65) Gallagher, P.H., Walsh, T.: The susceptibility of cereal varities to manganese deficiency; J. Agric. Sci., 33, 197-203, 1943.

66) McHargue, J.S., Lee, H.A.: The effect of manganese deficiency on the sugar cane plant and its relationship to fabala blight of sugar cane; Phytopath., 18, 775-788, 1928.

were based on chemical analyses of normal and chlorotic leaves and culture experiments. Chlorotic leaves contained no manganese in comparison with normal leaves and sugar cane grown on soil containing manganese developed normally but the plants grown without manganese developed Pahala Blight and eventually died. Plants belonging to the beet family -- sugar beet, red beet, spinach beet -- developed Speckled Yellows of Sugar Beet which was manifested by the appearance of yellow chlorotic areas in the leaves.

In 1936 Pethybridge (67) observed Marsh Spot of Peas, affecting pea plants grown in areas where oats developed Grey Speck. This led him to suspect that Marsh Spot could be attributed to manganese deficiency. In 1941 Piper (68) definitely related Marsh Spot to manganese deficiency by growing pea seeds under controlled culture conditions.

Manganese deficiency of the soil will cause similar diseases in citrus and other plants. Grey Speck, Pahala Blight, Speckled Yellows and Marsh Spot are known to occur in California, Florida, New England

---

67) Pethybridge, G.H.: Marsh spot in pea seeds; is it a deficiency disease? J. Minist. Agric., 43, 55-58, 1936.

68) Piper, C.S.: Marsh spot of peas: a manganese deficiency disease; J. Agric. Sci., 31, 448-453, 1941.

were based on chemical analyses of normal and chlorotic leaves and culture experiments. Chlorotic leaves contained no manganese in comparison with normal leaves and sugar cane grown on soil containing manganese developed normally but the plants grown without manganese developed Pahala Blight and eventually died. Plants belonging to the beet family -- sugar beet, red beet, spinach beet -- developed Speckled Yellows of Sugar Beet which was manifested by the appearance of yellow chlorotic areas in the leaves.

In 1938 Pethybridge (87) observed Marsh Spot of Peas, affecting pea plants grown in areas where oats developed Grey Speck. This led him to suspect that Marsh Spot could be attributed to manganese deficiency. In 1941 Piper (88) definitely related Marsh Spot to manganese deficiency by growing pea seeds under controlled culture conditions.

Manganese deficiency of the soil will cause similar diseases in citrus and other plants. Grey Speck, Pahala Blight, Speckled Yellows and Marsh Spot are known to occur in California, Florida, New England

---

87) Pethybridge, G.H.: Marsh spot in pea seeds; is it a deficiency disease? J. Minist. Agric., 45, 55-58, 1938.

88) Piper, C.S.: Marsh spot of peas: a manganese deficiency disease; J. Agric. Sci., 31, 449-453, 1941.

states and other areas in the United States. These diseases can be controlled by adding manganese salt to the soil and in some instances by spraying the foliage (69).

Animals

The wide distribution of manganese in the soil and its necessity for growth of plants has suggested that it is of equal importance for animals. Early investigators (70,71) have indicated that it may be necessary for animal nutrition. Orent and McCollum (72) first demonstrated the role of manganese in rats. They found that male rats weaned on a manganese deficient diet became sterile and developed testicular degeneration after three months. Female rats, on the same diet, produced offspring which survived for only a short time. Later work by Shils and McCollum (73) showed that

---

69) Harmer, P.M., Sherman, G.D.: The effect of manganese sulphate on several crops growing on organic soil when applied in solution or as a stream or spray on crop; Soil Sci. Soc. Amer. Proc., 8, 334-340, 1944.

70) McCarrison, R.: Effect of manganese on growth; Indian J. M. Rev., 14, 641-648, 1927.

71) McHargue, J.S.: Further evidence that small quantities of copper, manganese, and zinc are factors in the metabolism of animals; Am. J. Physiol., 77, 245-255, 1926.

72) Orent, E.R., McCollum, E.V.: Effects of deprivation of manganese in the rat; J. Biol. Chem., 92, 651-678,1931.

73) Shils, Maurice E., McCollum, E.V.: Further studies on the symptoms of manganese deficiency in the rat and mouse; J. Nutr., 26, 1-19, 1943.

states and other areas in the United States. These diseases can be controlled by adding manganese salt to the soil and in some instances by spraying the foliage (69).

Animals

The wide distribution of manganese in the soil and its necessity for growth of plants has suggested that it is of equal importance for animals. Early investigators (70,71) have indicated that it may be necessary for animal nutrition. Orent and McCollum (72) first demonstrated the role of manganese in rats. They found that male rats weaned on a manganese deficient diet became sterile and developed testicular degeneration after three months. Female rats, on the same diet, produced offspring which survived for only a short time. Later work by Smith and McCollum (73) showed that

---

69) Harmer, P.M., Sherman, G.D.: The effect of manganese sulphate in solution or as a stream or spray on crop: Soil Sci. Soc. Amer. Proc., 8, 334-340, 1944.

70) McCarrison, R.: Effect of manganese on growth; Indian J. M. Rev., 14, 641-648, 1927.

71) McHargue, J.S.: Further evidence that small quantities of copper, manganese, and zinc are factors in the metabolism of animals; Am. J. Physiol., 77, 485-488, 1926.

72) Orent, E.R., McCollum, E.V.: Effects of deprivation of manganese in the rat; J. Biol. Chem., 93, 651-678, 1931.

73) Smith, Maurice E., McCollum, E.V.: Further studies on the symptoms of manganese deficiency in the rat and mouse; J. Nutr., 26, 1-19, 1943.

manganese is essential for normal growth of the rat. The symptoms of deficiency are as follows:

(1) Female rats produce non-viable young.

(2) Deficient mice give birth to non-viable young.

(3) Female rats on a deficient diet late in pregnancy produce offspring which grow poorly.

(4) Deficient males are sterile and fail to grow normally.

These symptoms can be prevented and cured by the addition of manganese to the diets of rats and mice.

In 1937, Wilgus, Norris and Heuser (74) described a manganese deficiency in poultry known as Perosis. It is characterized by:

(1) poor bone formation -- causing a deformity of leg and wing bones;

(2) enlargement of the tibial-metatarsal joint.

In 1938, Gallup and Norris (75) confirmed these findings and also reported that chickens, hatched from eggs of hens fed on a manganese-deficient diet, had abnormally short and thick legs and short wings. These investigators reported that Perosis could be prevented by addition of manganese to the feed or by injecting

---

74) Wilgus, H.S., Norris, L.C., Heuser, G.F.: The role of manganese and certain other trace elements in the prevention of perosis; J. Nutr., 14, 155-167, 1937.

75) Gallup, W.D., Norris, L.C.: Essentialness of manganese for normal development of bone; Science, 87, 18-19, 1938.

manganese is essential for normal growth of the rat.

The symptoms of deficiency are as follows:

(1) Female rats produce non-viable young.

(2) Deficient mice give birth to non-viable young.

(3) Female rats on a deficient diet late in pregnancy produce offspring which grow poorly.

(4) Deficient males are sterile and fail to grow normally.

These symptoms can be prevented and cured by the addition of manganese to the diets of rats and mice.

In 1937, Wilgus, Norris and Heuser (74) described a manganese deficiency in poultry known as Perosis. It is characterized by:

(1) poor bone formation -- causing a deformity of leg and wing bones;

(2) enlargement of the tibial-metatarsal joint.

In 1938, Gallup and Norris (75) confirmed these findings and also reported that chickens, hatched from eggs of hens fed on a manganese-deficient diet, had abnormally short and thick legs and short wings. These investigators reported that Perosis could be prevented by addition of manganese to the feed or by injecting

---

74) Wilgus, H.S., Norris, L.C., Heuser, G.F.: The role of manganese and certain other trace elements in the prevention of perosis; J. Nutr., 14, 155-167, 1937.

75) Gallup, W.D., Norris, L.C.: Essentialness of manganese for normal development of bone; Science, 87. 18-19, 1938.

manganese into the egg before incubation. These studies (76) were conclusive for the hen feed contained all other essential elements (calcium, phosphorous, Vitamin D, etc., except manganese.

Similar to Perosis, bone abnormalities have been noted in rats (77) and pigs (78).

All of these investigators have concluded that manganese is essential for bone formation in the various species studied and it is quite likely that it may be essential for the development of bone in general.

Man

There is no definite knowledge of the requirements of manganese for man, nor is their evidence of any deficiency disease attributed to manganese deficiency. Studies by Kehoe and Cholak (79) show that 4 mg. manganese

---

76) Caskey, C.D., Gallup, W.D., Norris, L.C.: The need for manganese in the bone development of the chick; J. Nutr., 17, 407-417, 1939.

77) Barnes, L.L., Sperling, G., Maynard, L.A.: Bone development in the albino rat in a low manganese diet; Proc. Soc. Exper. Biol. & Med., 46, 562-565, 1941.

78) Miller, R.C., Keith, T.B., McCarthy, M.A., Thorp, W.T.: Manganese as a possible factor influencing the occurrence of lameness in pigs; Proc. Soc. Exper. Biol. & Med., 45, 50-51, 1940.

79) Kehoe, R.A., Cholak, J., Story, R.V.: Manganese,lead, tin, aluminum, copper and silver in normal biological material; J. Nutr., 20, 85-98, 1940.

manganese into the egg before incubation. These studies (76) were conclusive for the hen feed contained all other essential elements (calcium, phosphorous, Vitamin D, etc., except manganese.

Similar to Petosis, bone abnormalities have been noted in rats (77) and pigs (78).

All of these investigators have concluded that manganese is essential for bone formation in the various species studied and it is quite likely that it may be essential for the development of bone in general.

Man

There is no definite knowledge of the requirements of manganese for man, nor is their evidence of any deficiency disease attributed to manganese deficiency. Studies by Kehoe and Cholak (79) show that 4 mg. manganese

---

76) Cheney, G.D., Gallup, W.D., Norris, L.C.: The need for manganese in the bone development of the chick; J. Nutr., 17, 407-417, 1939.

77) Barnes, L.L., Sperling, G., Maynard, L.A.: Bone development in the albino rat in a low manganese diet; Proc. Soc. Exper. Biol. & Med., 48, 582-585, 1941.

78) Miller, R.C., Keith, T.B., McCarthy, M.A., Thorp, W.T.: Manganese as a possible factor influencing the occurrence of lameness in pigs; Proc. Soc. Exper. Biol. & Med., 45, 50-51, 1940.

79) Kehoe, R.A., Cholak, J., Story, R.V.: Manganese, lead, tin, aluminum, copper and silver in normal biological material; J. Nutr., 20, 85-98, 1940.

is found in daily human diets and that equal amounts are excreted. The greatest amounts of this element have been found in the liver, although its function in the body is unknown.

Hypothetical Remarks

The resemblance of bone changes found in Perotic animals have led some investigators to believe that the symptoms of slipped epiphyses in children are identical with Perosis. Further biochemical and histologic studies of these bone abnormalities should be extended before any definite conclusions can be drawn.

The relationship of manganese metabolism to arthritis deserves careful consideration.

is found in daily human diets and that equal amounts are excreted. The greatest amounts of this element have been found in the liver, although its function in the body is unknown.

Hypothetical Remarks

The resemblance of bone changes found in Peruvian animals have led some investigators to believe that the symptoms of clubbed epiphyses in children are identical with Perosis. Further biochemical and histologic studies of these bone abnormalities should be extended before any definite conclusions can be drawn.

The relationship of manganese metabolism to arthritis deserves careful consideration.

Table III

THE EPIDEMIOLOGY OF MANGANESE

Deficient Areas	Plant Diseases Grey Speck, Pahala Blight Speckled Yellous, Marsh Spot.	Animal Diseases (Deficiencies experimentally produced in the laboratory)
California	citrus fruits, peach, apricot.	Perosis of fowl
Florida	sugar cane, beans, corn, potatoes, citrus, tung.	Perosis of rabbits.
Kentucky	beans, peas	Lameness of pigs.
Maine	beets, celery	
Massachusetts	beets	
Michigan	beans, peas, beets	
Nevada	peaches, apricots	
New York	garden vegetables	
North Carolina	garden vegetables soy beans, oats	
Rhode Island	oats	
South Carolina	garden vegetables, cereals, soybeans	
Virginia	spinach	
Washington	peas, tomatoes	
Wisconsin	garden vegetables	

Table III

THE EPIDEMIOLOGY OF MANGANESE

Deficient Areas	Plant Diseases Grey Speck, Panama Blight Spoxied Yellows, Marsh Spot.	Animal Diseases (Deficiencies experimentally produced in the laboratory)
California	citrus fruits, peach, apricot.	Paroxia of fowl
Florida	sugar cane, beans, corn, potatoes, citrus, tung.	Paroxia of rabbits.
Kentucky	beans, peas	Lameness of pigs.
Maine	beets, celery	
Massachusetts	beets	
Michigan	beans, peas, beets	
Nevada	peaches, apricots	
New York	garden vegetables	
North Carolina	garden vegetables soy beans, oats	
Rhode Island	oats	
South Carolina	garden vegetables, cereals, soybeans	
Virginia	spinach	
Washington	peas, tomatoes	
Wisconsin	garden vegetables	

Chapter VII

ZINC

The Soil and Vegetation

Fruit growers have observed plant diseases due to zinc deficiency in the United States as early as 1900. In 1933 Finch and Kinnison (80) first described Pecan Rosette and found that pecan trees growing in zinc deficient soil in Arizona failed to develop normally, the leaves became chlorotic and mottled, the branches died and rosette buds developed below the dead region. In 1935 Reed and Dufrenoy (81) noticed that similar symptoms developed in the apricot, peach, tomato, maize and buckwheat. The soil was found deficient of zinc and after being treated with a zinc containing fertilizer, the plants recovered and continued to grow normally.

"Little Leaf," "Mottle Leaf" or "Yellows" are other plant diseases which are attributed to a zinc deficiency of the soil. These diseases have similar manifestations but have been variously termed by different

---

80) Finch, A.H., Kinnison, A.F.: Pecan mottle: soil chemical and physiological studies; Tech. Bull. Arizona Agric. Exp. Sta., 47, 407-442, 1933.

81) Reed, H.S., Dufrenoy, J.: The effects of zinc and iron salt on cell structure of mottled orange leaves; Hilgardia, 9, 113-137, 1935.

Chapter VII

ZINC

The Soil and Vegetation

Fruit growers have observed plant diseases due to zinc deficiency in the United States as early as 1900. In 1933 Finch and Kinnison (80) first described Pecan Rosette and found that pecan trees growing in zinc deficient soil in Arizona failed to develop normally, the leaves became chlorotic and mottled, the branches died and rosette buds developed below the dead region. In 1935 Reed and Durrenoy (81) noticed that similar symptoms developed in the apricot, peach, tomato, maize and buckwheat. The soil was found deficient of zinc and after being treated with a zinc containing fertilizer, the plants recovered and continued to grow normally.

"Little Leaf," "Mottle Leaf" or "Yellows" are other plant diseases which are attributed to a zinc deficiency of the soil. These diseases have similar manifestations but have been variously termed by different

---

80) Finch, A.H., Kinnison, A.F.: Pecan mottle: soil chemical and physiological studies; Tech. Bull. Arizona Agric. Exp. Sta., 47, 407-442, 1933.

81) Reed, H.S., Durrenoy, J.: The effects of zinc and iron salt on cell structure of mottled orange leaves; Hilgardia, 9, 113-137, 1935.

observers.

Little Leaf was described by Chandler, Hoagland and Hibbard (82) in 1932. The symptoms are similar to Pecan Rosette except the affected tree rarely dies, it nevertheless fails to produce fruit unless the soil is treated with zinc. In some instances a direct injection of zinc sulphate into the tree trunk aids in eliminating Little Leaf.

In 1933 Johnston (83) described Mottle Leaf affecting citrus trees in California. He found that Little Leaf of Deciduous Trees" occurred in the same orchards as Mottle Leaf in Citrus Trees and since zinc was used to cure the former condition, Johnston applied the same treatment for Mottle Leaf, whereupon the Citrus Trees improved and continued to grow.

A disease affecting corn (84), "White Bud of Maize," occurs in certain zinc deficient areas of Washington and Wisconsin. Successful treatment of the soil

---

82) Chandler, W.H., Hoagland, D.R., Hibbard, P.L.: Little-leaf or rosette in fruit trees; Proc. Amer. Soc. Hort. Sci., 28, 556-560, 1932.

83) Johnston, J.C.: Zinc Sulfate--promising new treatment for mottle leaf; Calif. Citrograph, 18, 116-118, 1933.

84) Barnetts, R.M., Warner, J.D.: A response of chlorotic corn plants to the application of zinc sulphate to the soil; Soil Sci., 39, 146-156, 1935.

observers.

Little Leaf was described by Chandler, Hoagland and Hibbard (82) in 1932. The symptoms are similar to Pecan Rosette except the affected tree rarely dies, it nevertheless fails to produce fruit unless the soil is treated with zinc. In some instances a direct injection of zinc sulphate into the tree trunk aids in eliminating Little Leaf.

In 1933 Johnston (83) described Mottle Leaf affecting citrus trees in California. He found that Little Leaf of Deciduous Trees" occurred in the same orchards as Mottle Leaf in Citrus Trees and zinc was used to cure the former condition, Johnston applied the same treatment for Mottle Leaf, whereupon the Citrus Trees improved and continued to grow.

A disease affecting corn (84), "White Bud of Maize," occurs in certain zinc deficient areas of Washington and Wisconsin. Successful treatment of the soil

---

82) Chandler, W.H., Hoagland, D.R., Hibbard, P.L.: Little-leaf or rosette in fruit trees; Proc. Amer. Soc. Hort. Sci., 28, 556-560, 1932.

83) Johnston, J.C.: Zinc Sulfate--promising new treatment for mottle leaf; Calif. Citrograph, 18, 118-118, 1933.

84) Barnette, R.M., Warner, J.D.: A response of chlorotic corn plants to the application of zinc sulphate to the soil; Soil Sci., 39, 149-156, 1935.

with zinc containing fertilizers has been reported from these states as well as areas in Florida, Texas, Louisiana, New Zealand and South Africa.

Animals

Although no diseases in animals have been definitely associated with a zinc deficiency, Todd, Elvehjem and Hart (85) in 1934 showed that mice require zinc for normal development. These investigators found that rats fed on a zinc deficient diet showed the following symptoms:

(1) impaired growth

(2) alopecia

(3) anorexia

(4) inanition

(5) death

This picture could be reversed by addition of zinc to the diet. These findings have been confirmed by various authors and it is now agreed that zinc is indispensable for growth in mice and rats.

In 1940 Keilin and Mann (86) found that ox-carbonic anhydrase contained .31% of zinc. This was first the concrete evidence of the role which zinc plays in

---

85) Todd, W.R., Elvehjem, C.A., Hart, E.B.: Zinc in the nutrition of the rat; Am.J.Physiol., 107, 146-156,1934.

86) Keilin, D., Mann, T.: Carbonic anhydrase, purification and nature of the enzyme; Biochem.J.,34,1163, 1940.

with zinc containing fertilizers has been reported from these states as well as areas in Florida, Texas, Louisiana, New Zealand and South Africa.

Animals

Although no diseases in animals have been definitely associated with a zinc deficiency, Todd, Elvehjem and Hart (85) in 1934 showed that mice require zinc for normal development. These investigators found that rats fed on a zinc deficient diet showed the following symptoms:

(1) impaired growth

(2) alopecia

(3) anorexia

(4) inanition

(5) death

This picture could be reversed by addition of zinc to the diet. These findings have been confirmed by various authors and it is now agreed that zinc is indispensable for growth in mice and rats.

In 1940 Keilin and Mann (88) found that carbonic anhydrase contained .31% of zinc. This was first the concrete evidence of the role which zinc plays in

---

85) Todd, W.R., Elvehjem, C.A., Hart, E.B.: Zinc in the nutrition of the rat; Am.J.Physiol., 107, 146-156,1934.

86) Keilin, D., Mann, T.: Carbonic anhydrase, purification and nature of the enzyme; Biochem.J., 34,1163, 1940.

mammalian physiology. This enzyme catalyzes the reaction $H_2CO_3 \rightleftharpoons H_2O + CO_2$.

Previous reports that insulin contains zinc (87) have not been confirmed.

Man

In 1947 Vallee (88) reported that zinc is a constituent of white blood cells, and the following year he observed that leukemic white blood cells contained only 10% of their normal zinc complement.

Hypothetical Remarks

The relationship of zinc to leukemia deserves further consideration and may reveal important information. It may be assumed that zinc deficiency states in man do exist. A system as complex and yet important as Carbonic Anhydrase may well break down either due to lack of zinc or of the prosthetic group. The resulting pathological syndrome cannot be predicted on the basis of presently available data.

---

87) Scott, D.A., Fisher, A.M.: Crystalline insulin; Biochem. J., 29, 1048-1054, 1935.

88) Vallee, B.L., Fluharty, R.G.: Zinc metabolism studied by means of the radioactive isotope; $_{30}Zn^{65}$; J. Clin. Invest., 26, 1199, 1947.

mammalian physiology. This enzyme catalyzes the reaction $H_2CO_3 \rightleftarrows H_2O + CO_2$.

Previous reports that insulin contains zinc (87) have not been confirmed.

Man

In 1942 Vallee (88) reported that zinc is a constituent of white blood cells, and the following year be observed that leukemic white blood cells contained only 10% of their normal zinc complement.

Hypothetical Remarks

The relationship of zinc to leukemia deserves further consideration and may reveal important information. It may be assumed that zinc deficiency states in man do exist. A system as complex and yet important as Carbonic Anhydrase may well break down either due to lack of zinc or of the prosthetic group. The resulting pathological syndrome cannot be predicted on the basis of presently available data.

---

87) Scott, D.A., Fisher, A.M.: Crystalline insulin: Biochem. J., 39, 1048-1054, 1938.

88) Vallee, B.L., Flaherty, R.G.: Zinc metabolism in study by means of the radioactive isotope: $^{30}Zn^{65}$; J. Clin. Invest., 28, 1199, 1947.

Table IV.

THE EPIDEMIOLOGY OF ZINC

Deficient Areas	Plant Diseases Pecan Rosette, Little Leaf, Mottle Leaf	Animal Diseases (Deficiencies experimentally produced in the Laboratory.
Arizona	pecans	Failure of growth in rats and mice.
California	citrus fruits, grapes, peas	
Florida	citrus fruits, peaches	
South Carolina	pecans	
Texas	pecans	
Washington	apples	
Wisconsin	sweet corn	

Table IV.

THE EPIDEMIOLOGY OF ZINC

Deficient Areas	Plant Diseases	Animal Diseases
	Pecan Rosette, Little Leaf, Mottle Leaf	(Deficiencies experimentally produced in the laboratory.
Arizona	pecans	Failure of growth in rats and mice.
California	citrus fruits, grapes, peas	
Florida	citrus fruits, peaches	
South Carolina	pecans	
Texas	pecans	
Washington	apples	
Wisconsin	sweet corn	

Chapter VIII

MOLYBDENUM

The Soil and Vegetation

In 1932 (89) Ter Meulen made analyses of various plants and found molybdenum present in higher plants. He further analyzed various soils and found that productive soils had a higher molybdenum content than soils of low capacity for crop production. In 1939 Arnon and Stout (90) grew tomato plants in molybdenum free culture and reported that deficiency symptoms developed. The plant leaves appeared mottled, became necrotic and finally died. They observed a similar condition in barley and lettuce and found that the deficiency symptoms in each instance disappeared with the addition of molybdenum. In 1940 Hoagland (91) found that plum seedlings were affected when grown in a molybdenum-free culture.

---

89) Ter Meulen, H.: Distribution of Molybdenum; Nature, 130, 966, 1932.

90) Arnon, D.J., Stout, P.R.: Molybdenum as an essential element for higher plants; Plant Physiol, 14, 599-602, 1939.

91) Hoagland, D.R.: Water-culture experiments on molybdenum and copper deficiencies in fruit trees; Proc. Amer. Soc. Hort. Sci., 38, 8-12, 1940.

Chapter VIII

MOLYBDENUM

The Soil and Vegetation

In 1932 (89) Ter Meulen made analyses of various plants and found molybdenum present in higher plants. He further analyzed various soils and found that productive soils had a higher molybdenum content than soils of low capacity for crop production. In 1939 Arnon and Stout (90) grew tomato plants in molybdenum free culture and reported that deficiency symptoms developed. The plant leaves appeared mottled, became necrotic and finally died. They observed a similar condition in barley and lettuce and found that the deficiency symptoms in each instance disappeared with the addition of molybdenum. In 1940 Hoagland (91) found that plum seedlings were affected when grown in a molybdenum-free culture.

---

89) Ter Meulen, H.: Distribution of Molybdenum; Nature, 130, 986, 1932.

90) Arnon, D.I., Stout, P.R.: Molybdenum as an essential element for higher plants; Plant Physiol., 14, 599-602, 1939.

91) Hoagland, D.R.: Water-culture experiments on molybdenum and copper deficiencies in fruit trees; Proc. Amer. Soc. Hort. Sci., 38, 8-12, 1940.

While all this previous work was done in artificial cultures, Piper (92) was the first one to notice a molybdenum deficiency in nature. In Australia, he observed that molybdenum was essential for the growth of oats since they failed to produce grain when grown on molybdenum-free soil and with the addition of molybdenum the grain yield increases significantly. In 1942 Anderson (93) reported a similar deficiency disease in alfalfa grown in soils in South Australia.

Animals

In contrast to the other elements which have been discussed, molybdenum does not cause a deficiency disease in animals, instead pastures containing an excessive amount of this element cause an intoxication disease known as Scouring. Scouring in cattle has been observed in Somerset, Gloucestershire and Warwickshire for many years. It had been attributed to such factors as herbage species, bacteria, contamination of water supply and poor soil. In 1943 Ferguson, Lewis and Watson (94) made spectrographic analyses of the herbage and

---

92) Piper, C.S.: Molybdenum as an essential element for plant growth; Jour. Aust. Inst. Agr. Sci., 6, 162-164, 1940.

93) Anderson, A.J.: Molybdenum deficiency on a South Australian ironstone soil; Jour. Aust. Inst. Agr. Sci, 8, 73-75, 1942.

94) Ferguson, W.S., Lewis, A.H., Watson, S.J.: The teart pastures of Somerset. I. The cause and cure of teartness; J. Agric.Sci., 33, 44-51, 1943.

While all this previous work was done in artificial cultures, Piper (92) was the first one to notice a molybdenum deficiency in nature. In Australia, he observed that molybdenum was essential for the growth of oats since they failed to produce grain when grown on molybdenum-free soil and with the addition of molybdenum the grain yield increases significantly. In 1942 Anderson (93) reported a similar deficiency disease in alfalfa grown in soils in South Australia.

Animals

In contrast to the other elements which have been discussed, molybdenum does not cause a deficiency disease in animals, instead pastures containing an excessive amount of this element cause an intoxication disease known as Scouring. Scouring in cattle has been observed in Somerset, Gloucestershire and Warwickshire for many years. It had been attributed to such factors as herbage species, bacteria, contamination of water supply and poor soil. In 1943 Ferguson, Lewis and Watson (94) made spectrographic analyses of the herbage and

---

92) Piper, C.S.: Molybdenum as an essential element for plant growth; Jour. Aust. Inst. Agr. Sci., 5, 152-154, 1940.

93) Anderson, A.J.: Molybdenum deficiency on a South Australian ironstone soil; Jour. Aust. Inst. Agr. Sci, 8, 73-75, 1942.

94) Ferguson, W.S., Lewis, A.H., Watson, S.J.: The teart pastures of Somerset. I. The cause and cure of teartness; J. Agric.Sci., 33, 44-51, 1943.

found the molybdenum content to be much higher in areas where Scouring occurred, by comparison with the herbage in non-affected areas. Further studies by these investigators showed that Scouring in cattle could be induced by administration of large doses of molybdenum. In areas where certain herbage, especially clover, absorbs a large amount of molybdenum the cattle develop symptoms of Scouring readily. This is characterized by:

(1) appearance of degeneration -- animals become filthy;

(2) coats lose shiny luster;

(3) diarrhea and weakness.

Scouring is treated effectively by addition of copper sulphate to the forage of cattle. Copper sulphate fertilization of pastures containing excess molybdenum decreases the severity of the disease for plants absorb less molybdenum. These phenomena are not explained at present but indicate interrelations between various elements.

Man

The function of molybdenum in man is completely unknown.

found the molybdenum content to be much higher in areas where scouring occurred, by comparison with the herbage in non-affected areas. Further studies by these investigators showed that scouring in cattle could be induced by administration of large doses of molybdenum. In areas where certain herbage, especially clover, absorbs a large amount of molybdenum the cattle develop symptoms of scouring readily. This is characterized by:

(1) appearance of degeneration -- animals become filthy;

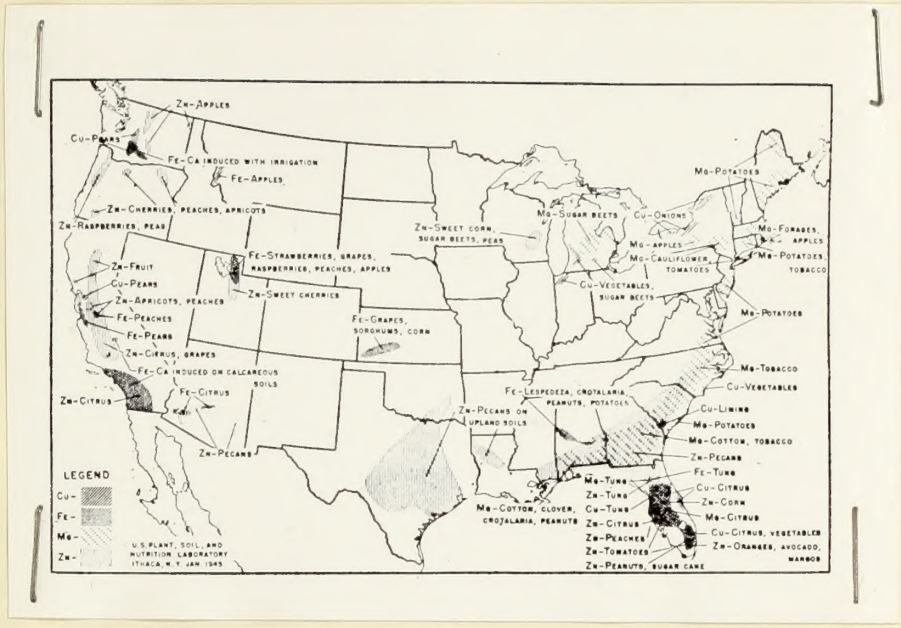
(2) costs lose shiny luster;

(3) diarrhea and weakness.

Scouring is treated effectively by addition of copper sulphate to the forage of cattle. Copper sulphate fertilization of pastures containing excess molybdenum decreases the severity of the disease for plants absorb less molybdenum. These phenomena are not explained at present but indicate interrelations between various elements.

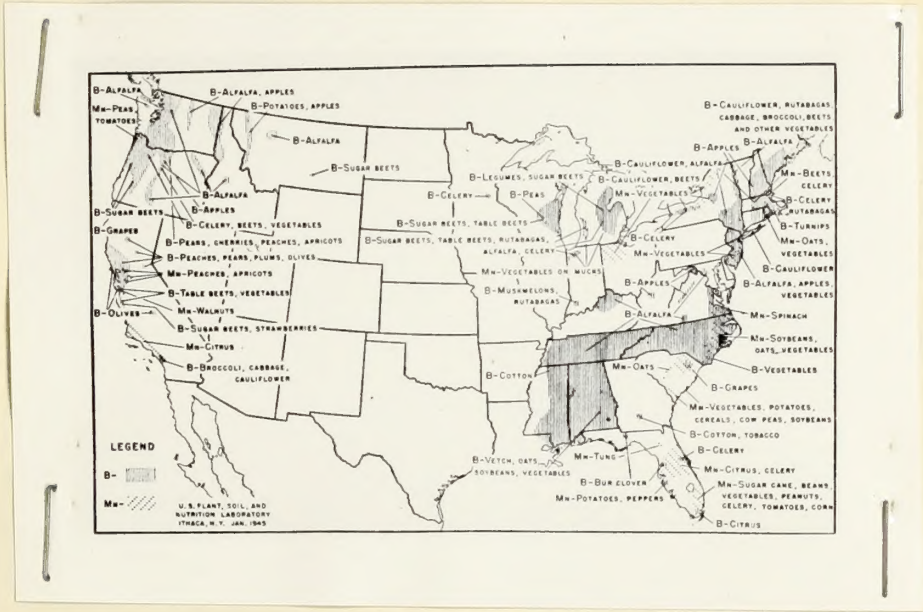
Man

The function of molybdenum in man is completely unknown.



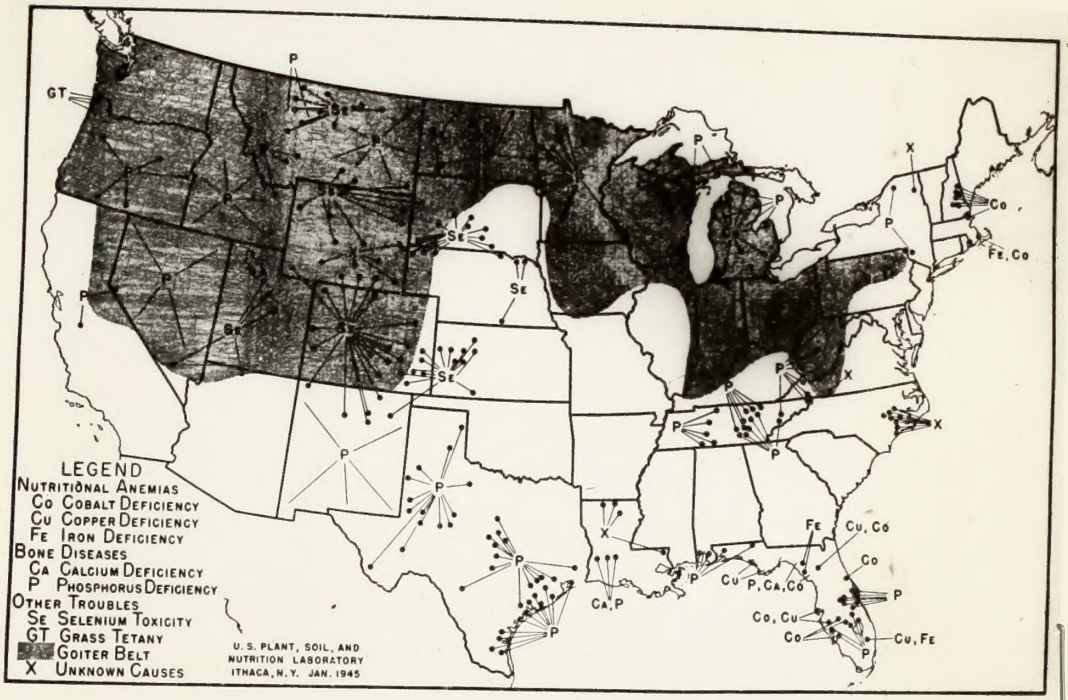
Generalized map of the occurrence of Copper, Iron, Magnesium and Zinc deficiencies in plants. Although the deficient areas are necessarily shown as continuous, they are actually intermittent in character. Modification of these areas will be possible as more data become available.

(Beeson, Kenneth C.: The occurrence of mineral nutritional diseases of plants and animals in the United States; Soil Science, 60, 10, 1945.)



Generalized map of the occurrence of Boron and Manganese deficiencies in plants. Although the deficient areas are necessarily shown as continuous, they are actually intermittent in character. Modification of these areas will be possible as more data become available.

(Beeson, Kenneth C.: The occurrence of mineral nutritional diseases of plants and animals in the United States; Soil Science, 60, 10, 1945.)



Occurrence of mineral nutritional diseases in animals. The data show the approximate location of observed deficiency. The lines not terminating in dots indicate a generalized area where specific locations have not been reported. The goiter region is also a generalized area.

(Beeson, Kenneth C.: The occurrence of mineral nutritional diseases of plants and animals in the United States; Soil Science, 60, 10, 1945.)

Chapter IX

DISCUSSION AND SUMMARY

The data presented on five elements clearly establish their essentiality in many biological systems. The circumstantial evidence is sufficient to warrant the assumption that they play a major role in human physiology and pathology. In some instances this has been established, but not nearly to the point which would be desirable.

As in the case of iodine and fluorine, the physiopathology of certain conditions could be correlated statistically with the geographic distribution of elements. The relationship of copper intake to Multiple Sclerosis and Syringomyelia would seem like a particularly intriguing problem of sufficient importance to warrant the effort of investigation.

Availability of Data

Soil data: (a) From various parts of the United States will have to be obtained from the U.S. Department of Agriculture and the States. The three accompanying maps(95)

---

95) Beeson, Kenneth C.: The occurrence of mineral nutritional diseases of plants and animals in the United States; Soil Science, 60, 10, 1945.

Chapter IX

DISCUSSION AND SUMMARY

The data presented on five elements clearly establish their essentiality in many biological systems. The circumstantial evidence is sufficient to warrant the assumption that they play a major role in human physiology and pathology. In some instances this has been established, but not nearly to the point which would be desirable.

As in the case of iodine and fluorine, the physiopathology of certain conditions could be correlated statistically with the geographic distribution of elements. The relationship of copper intake to Multiple Sclerosis and Syringomyelia would seem like a particularly intriguing problem of sufficient importance to warrant the effort of investigation.

Availability of Data

Soil data: (a) From various parts of the United States will have to be obtained from the U.S. Department of Agriculture and the States. The three accompanying maps(95)

---

95) Beeson, Kenneth C.: The occurrence of mineral nutritional diseases of plants and animals in the United States; Soil Science, 60, 10, 1945.

illustrate the present state of knowledge on metal soil distribution in the United States.

(b) The Soil Bureau of the Australian Government has already consented to supply such information on Australian soil.

Data on Plants and Animals:

As in (a) and (b) above.

Data on Man:

(a) Vital statistics will be obtained from the U.S. Public Health Service. This service is at present conducting a special survey on the Vital Statistics of Multiple Sclerosis, trying to encompass all of the United States. These data should be reliable and medically accurate. They will be made available for such a future study.

(b) Similar data will be obtained from the Australian Government.

Statistics:

This information will have to be correlated statistically by calculation of coefficients of correlation. Whether the correlation is positive or negative will not detract from the value of such a study, since confirmation or elimination of this clue

illustrate the present state of knowledge on metal soil distribution in the United States.

(b) The Soil Bureau of the Australian Government has already consented to supply such information on Australian soil.

Data on Plants and Animals:

As in (a) and (b) above.

Data on Man:

(a) Vital statistics will be obtained from the U.S. Public Health Service. This service is at present conducting a special survey on the Vital Statistics of Multiple Sclerosis, trying to encompass all of the United States. These data should be reliable and medically accurate. They will be made available for such a future study.

(b) Similar data will be obtained from the Australian Government.

Statistics:

This information will have to be correlated statistically by calculation of coefficients of correlation. Whether the correlation is positive or negative will not detract from the value of such a study, since confirmation or elimination of this clue

will both clarify the quest for the solution of the Multiple Sclerosis problem.

Pilot experiment:

In order to undertake a test experiment on a smaller scale than presented above, authorities of the State of New York have been contacted and have declared their willingness to cooperate in the following fashion:

(1) Dr. Kenneth C. Beeson, Director U.S. Soil Bureau at Ithaca, will make available soil, plant and animal data for the State of New York.

(2) Drs. Gilbert Dalldorf and Morton Levin of the N.Y. State Health Division have agreed to supply the vital statistics for the State of New York.

(3) If desirable to limit the investigation to a specific area, they as well as the authorities of the Mary Imogene Bassett Hospital at Cooperstorm, N.Y., will assist in the evaluation of that hospital's records, representing a typical rural population in that state.

Experimental Limitations

It is fully realized that there are several handicaps to an investigation of this type.

(a) Vital statistics as kept by states and federal agencies are often inaccurate. This should be largely

will both clarify the quest for the solution of the
Multiple Sclerosis problem.

Pilot experiment:

In order to undertake a test experiment on a
smaller scale than presented above, authorities of the
State of New York have been contacted and have declared
their willingness to cooperate in the following fashion:

(1) Dr. Kenneth C. Beeson, Director U.S. Soil
Bureau at Ithaca, will make available soil, plant and
animal data for the State of New York.

(2) Drs. Gilbert Daldorf and Morton Levin of the
N.Y. State Health Division have agreed to supply the
vital statistics for the State of New York.

(3) If desirable to limit the investigation to a
specific area, they as well as the authorities of the
Mary Imogene Bassett Hospital at Cooperstown, N.Y.,
will assist in the evaluation of that hospital's records,
representing a typical rural population in that state.

Experimental Limitations

It is fully realized that there are several
handicaps to an investigation of this type.

(a) Vital statistics as kept by states and federal
agencies are often inaccurate. This should be largely

overcome by utilizing the data of the special Multiple Sclerosis study.

(b) Modern living has brought about consumption of foods from all parts of the country and the world. This is less likely to play a role in rural states where the population lives off the land. The Australian data should aid in eliminating this factor, since they represent a relatively isolated area.

(c) Similar reasoning as in (b) applies to population shifts.

The plan has been discussed with several statisticians and Public Health authorities and has been found feasible by them. This fact has greatly encouraged the writer to submit this hypothesis and suggest it for further study.

overcome by utilizing the data of the special Multiple Sclerosis study.

(b) Modern living has brought about consumption of foods from all parts of the country and the world. This is less likely to play a role in rural states where the population lives off the land. The Australian data should aid in eliminating this factor, since they represent a relatively isolated area.

(c) Similar reasoning as in (b) applies to population shifts.

The plan has been discussed with several statisticians and Public Health authorities and has been found feasible by them. This fact has greatly encouraged the writer to submit this hypothesis and suggest it for further study.

BIBLIOGRAPHY

1) Baumann, E., Ztshrft. Physiol. Chem., 21, 319, 1895-1896.

2) McHargue, J.S., Young, D.W., Calfee, R.K, J. Amer. Soc. Agron., 27, 559-565, 1935.

3) McHargue, J.S., Roy, W.R., Pelphrey, J.G., Amer. Fertilizer, 73, 46-63, 1930.

4) McHarg, O., Milk Dealer, 24, 7, 76-80, 1935.

5) Asmundson, V.S., Almquist, H.J., Klose, A.A., J. of Nutr., 12, 1-14, 1936.

6) Smith, M.C., Lantz, E.M., Smith, H.V., Arizona Agr. Expt. Sta. Tech. Bull., 32, 254-282, 1941.

7) Lantz, E. M., Smith, H.V., J. Amer. Dental Assoc., 22 817-829, 1935.

8) Smith, M. C., Osborn, F.E., Arizona Agr. Expt. Sta. Tech. Bull., 61, 373-418, 1936.

9) Bull, F.A., J. Amer. Dental Assoc., 30, 1206-1215, 1943.

10) Deathrage, C.F., J. Dental Research, 22, 173-180, 1943.

11) Mitchell, H.H., Edman, M., Soil Science, 60, 81-90, 1945.

12) Blakemore, F., Proc. Nutr. Soc., 1, 211-215, 1944.

13) Smith, M.C., Yearbook of Agr. U.S. Govt.Printing Office, Washington, D.C., 212-213, 1939.

14) Armstrong, W.D., J.B.C., V, 119, 1937.

15) Armstrong, W.D., Berkhus, P.J., J. Dent. Res., 17, 393, 1938.

16) Floyd, B.F., Bull. Fla. Agric. Exp. Sta., No. 140, p. 1-31, 1917.

17) Smith, R.E., Thomas, H.E., Phytopathology, 18, 449-54.

18) Sommer, A.L., Amer. Fert., 72, No. 6, p. 15-18, 1930.

BIBLIOGRAPHY

1) Baumann, E., Ztschrft. Physiol. Chem., 21, 319, 1895-1896.

2) McHargue, J.S., Young, D.W., Calfee, R.K., J. Amer. Soc. Agron., 27, 559-565, 1935.

3) McHargue, J.S., Roy, W.R., Pelphrey, J.O., Amer. Fertilizer, 73, 46-63, 1930.

4) McHarg, O., Milk Dealer, 24, 7, 76-80, 1935.

5) Asmundson, V.S., Kimpwiet, H.J., Klose, A.A., J. of Nutr., 12, 1-14, 1936.

6) Smith, M.C., Lantz, E.M., Smith, H.V., Arizona Agr. Expt. Sta. Tech. Bull., 32, 254-282, 1941.

7) Lantz, E. M., Smith, H.V., J. Amer. Dental Assoc., 23, 817-829, 1936.

8) Smith, M. C., Osborn, F.E., Arizona Agr. Expt. Sta. Tech. Bull., 61, 373-418, 1935.

9) Bull, F.A., J. Amer. Dental Assoc., 30, 1806-1818, 1943.

10) Deathrage, C.F., J. Dental Research, 22, 173-180, 1943.

11) Mitchell, H.H., Edman, M., Soil Science, 50, 81-90, 1940.

12) Blakemore, F., Proc. Nutr. Soc., 1, 211-215, 1944.

13) Smith, M.C., Yearbook of Agr. U.S. Govt. Printing Office, Washington, D.C., 213-213, 1939.

14) Armstrong, W.D., J.B.C., V, 119, 1937.

15) Armstrong, W.D., Berkhus, P.J., J. Dent. Res., 17, 393, 1938.

16) Floyd, R.F., Bull. Fla. Agric. Exp. Sta., No. 1440, p. 1-31, 1917.

17) Smith, R.E., Thomas, H.E., Phytopathology, 18, 449-64.

18) Sommer, A.L., Amer. Fert., 73, No. 6, p. 15-18, 1930.

19) Sommer, A.L., Plant Physiol., 6, 339-345, 1931.

20) Haas, A.R.C., Quayle, H.J., Hilgardia, 9, 143-177, 1935.

21) Sjollema, B., Biochem. Z., 267, 151-156, 1933.

22) Brandenburg, E., II Tijdschr. Plziekt. 39, 189-192, 1933.

23) Piper, C.S., J. Agric. Sci., 32, 143-178, 1942.

24) Teakle, L.J.H., J. Dept. Agr. West. Aust., 19, 242-253, 1942.

25) Anderssen, F.G., J. Pomol. and Hort. Sci., 10, 130-146, 1932.

26) Rademacher, B., Forschr. Landw. Chem. Forsch., 149-160, 1937.

27) Hart, E.B., Steenbock, H., Waddell, J., Elvehjem, C.A., J. Biol. Chem., 77, 797-812, 1928.

28) McHargue, J.S., Healy, D.J., Hill, E.S., J. Biol. Chem., 78, 637-641, 1928.

29) Becker, R.B., Neal, W.M., Shealy, A.L., Bull. Fla. Agric. Exp. Sta., No. 231, p. 1-22, 1931.

30) Stewart, W.L., Vet. J., 88, 133-137, 1932.

31) Bennets, H.W., Aust. Vet. J., 8, 137-142; 183-184, 1932.

32) Dunlop, G., Innes, J.R.M., Shearer, G.D., and Wells, H., J. Comp. Path., 52, 259-265, 1939.

33) Dunlop, G. Wells, H.E., Vet. Rec., 50, 1175-1182, 1938.

34) Elvehjem, C.A., Hart, E.B., J. Biol. Chem., 32, 473-477, 1929.

35) Josephs, H., Bull. Johns Hopkins Hosp., 49, 246-258, 1931.

36) Elvehjem, C.A., Duckles, D., Mendenhall, D.R., Amer. J. Diseases Children, 53, 785-793, 1937.

19) Sommer, A.L., Plant Physiol., 6, 339–346, 1931.

20) Haas, A.R.G., Quayle, H.J., Hilgardia, 9, 143–177, 1935.

21) Stoltzenberg, R., Biochem. Z., 267, 151–156, 1933.

22) Trendenburg, E., II Tijdschr. Plziekt. 39, 189–192, 1933.

23) Piper, C.S., J. Agric. Sci., 32, 143–178, 1942.

24) Tenkle, L.J.H., J. Dept. Agr. West. Aust., 19, 242–253, 1942.

25) Andersson, F.G., J. Pomol. and Hort. Sci., 10, 130–146, 1932.

26) Rademacher, B., Forschr. Landw. Chem. Forsch., 149–180, 1937.

27) Hart, E.B., Steenbock, H., Waddell, J., Elvehjem, C.A., J. Biol. Chem., 77, 797–812, 1928.

28) McHargue, J.S., Healy, D.J., Hill, E.S., J. Biol. Chem., 78, 637–641, 1928.

29) Hooker, R.B., Neal, W.M., Sheely, A.I., Bull. Pla. Agric. Exp. Sta., No. 231, p. 1–32, 1931.

30) Stewart, W.L., Vet. J., 88, 133–137, 1932.

31) Bennets, H.W., Aust. Vet. J., 8, 137–142; 183–184, 1932.

32) Dunlop, G., Innes, J.R.M., Shearer, G.D., and Wells, H., J. Comp. Path., 52, 259–265, 1939.

33) Dunlop, G. Wells, H.E., Vet. Rec., 50, 1175–1182, 1938.

34) Elvehjem, C.A., Hart, E.B., J. Biol. Chem., 78, 473–477, 1928.

35) Josephs, H., Bull. Johns Hopkins Hosp., 49, 346–358, 1931.

36) Elvehjem, C.A., Duckles, D., Mendenhall, D.F., Amer. J. Diseases Children, 53, 785–793, 1937.

37) Mann, T., Keilin, D., Proc. Roy. Soc., B. 126, 303-315, 1938.

38) Hurwitz, C., Beeson, Kenneth C., Food Research, 9, 348-357, 1944.

39) Hogg, J., Quart. J. Agric., 2, 697-706, 1831.

40) Greig, J.R., Dryene, H., Godden, W., Crichton, A., Ogg, W.G., Vet. J., 89, 99-110, 1933.

41) Asken, H.D., Dixon, J.K., New Zealand J. Sc. Technol., 18, 73-84, 1936.

42) Wunsh, D.S., Chem. and Ind., 15, 855-859, 1937.

43) Underwood, E.J., Filmer, J.F., Australian Vet. J., 11, 84-92, 1935.

44) Filmer J.F., Underwood, E.J., Aust. Vet.J.,13, 57-64, 1937.

45) Underwood, E.J., Harvey, R.J., Aust. Vet. J., 14, 183-189, 1938.

46) Kidson, E.B., Maunsell, P.W., N.Z. J. Sci. Tech., 21A, 125-128, 1939.

47) Comer, H.H., Smith, A.M., Biochem. J., 32, 1800-1805, 1938.

48) Stewart, J., Mitchell, R.L., Stewart, A.B., Empire J. Exp. Agric., 9, 145-52, 1941.

49) Bowstead, J.E., Sackville, J.P., Canad. J. Res., 17, 15-28, 1939.

50) McIntosh, R.A., Canad. J. Compar. Med. and Vet. Sci., 9, 179-182, 1945.

51) Baltzer, A.C., Killham, B.J., Duncan, C.W., Huffman, C.F., Mich. Agr. Expt. Sta. Quart. Bull., 24, 68-70, 1941.

52) Archibald, J.G., Bennett, E., Mass. Agr. Expt. Sta. Bull., 300, 1-7, 1933.

53) Keener, H.A., Percival, G.P., Morrow, K.S., New Hampshire Sta. Cir. 68, 1-8, 1944.

37) Mann, T., Kellin, D., Proc. Roy. Soc., B. 128, 303-316, 1939.

38) Hurwitz, C., Pegson, Kenneth C., Food Research, 9, 349-357, 1944.

39) Hoff, J., Quart. J. Agric., 8, 697-706, 1937.

40) Greig, J.R., Dryene, H., Godden, W., Gretchton, A., Oeg, W.G., Vet. J., 89, 99-110, 1933.

41) Asken, H.D., Dixon, J.K., New Zealand J. Sc. Technol., 18, 73-84, 1939.

42) Wunah, D.S., Chem. and Ind., 15, 855-859, 1937.

43) Underwood, E.J., Filmer, J.F., Australian Vet. J., 11, 84-92, 1935.

44) Filmer J.F., Underwood, E.J., Aust. Vet.J.,13, 57-64, 1937.

45) Underwood, E.J., Harvey, R.J., Aust. Vet. J., 14, 183-189, 1938.

46) Kidson, E.B., Maunsell, P.W., N.Z. J. Sci. Tech., 21A, 128-138, 1939.

47) Comer, H.H., Smith, A.M., Biochem. J., 32, 1800-1805, 1938.

48) Stewart, J., Mitchell, R.L., Stewart, A.B., Empire J. Exp. Agric., 9, 145-52, 1941.

49) Bowstead, J.E., Sackville, J.P., Canad. J. Res., 17, 15-28, 1939.

50) McIntosh, R.A., Canad. J. Comper. Med. and Vet. Sci., 9, 179-182, 1945.

51) Baltzer, A.C., Killiam, B.J., Duncan, C.W., Hurlman, C.F., Mich. Agr. Expt. Sta. Quart. Bull., 24, 68-70, 1941.

52) Archibald, J.G., Bennett, E., Mass. Agr. Expt. Sta. Bull., 300, 1-7, 1933.

53) Keener, H.A., Percival, G.P., Morrow, K.S., New Hampshire Sta. Cir. 58, 1-8, 1944.

54) Lyford, W.H., Jr., Percival, G.P., Keener, H.A., Morrow, K.S., Soil Sci. Am. Proc., 10, 375-380, 1945.

55) Beeson, K. C., Gray, L., Smith, S.E., Soil Sci. Am. Proc., 9, 164-168, 1944.

56) Stare, F.J. Elvehjem, C.A., J. Biol. Chem., 99, 473-483, 1933.

57) Waltner, K., Waltner, K., Wchnschr., 8, 313, 1929.

58) Orten, J.M., Underhill, F.A., Mugrage, E.R., Lewis, R.C., J. Biol. Chem., 96, 11-16, 1932.

59) Rickes, E.L., Brink, N.G., Koniuszy, F.R., Wood, T.R., Folkers, K., Science, 108, 134, 1948.

60) Bertrand, G., C. R. Acad. Sci. Paris, 124, 1032-1035, 1355-1358, 1897.

61) McHargue, J.S., Jour. Amer. Chem. Soc., 36, 2532-2536, 1914.

62) Samuel, G., Piper, C.S., J. Agric. S. Aust., 31, 696-705, 789-799, 1928.

63) Samuel, G., Piper, C.S., Ann. Appl. Biol., 16, 493-524, 1929.

64) Pettinger, N.A., Henderson, R.G., Wingard, A., Phytopathology, 22, 33-51, 1932.

65) Gallagher, P.H., Walsh, T., J. Agric. Sci., 33, 197-203, 1943.

66) McHargue, J.S., Lee, H.A., Phytopath., 18, 775-786, 1928.

67) Pethybridge, G.H., J. Minist. Agric., 43, 55-58, 1936.

68) Piper, C.S., J. Agric. Sci., 31, 448-453, 1941.

69) Harmer, P. M., Sherman, G.D., Soil Sci. Soc. Amer. Proc., 8, 334-340, 1944.

70) McCarrison, R., Indian J. M. Rev., 14, 641-648, 1927.

54) Lyford, W.H., Jr., Petroval, O.P., Keener, R.A., Morrow, K.S., Soil Sci. Am. Proc., 10, 375-380, 1945.

55) Peeson, K. C., Gray, L., Smith, S.E., Soil Sci. Am. Proc., 9, 164-168, 1944.

56) Stare, F.J. Elvehjem, C.A., J. Biol. Chem., 99, 473-483, 1933.

57) Waltner, K., Waltner, K., Wohnsohr., 8, 313, 1939.

58) Otten, J.M., Underhill, T.A., Mugrage, E.R., Lewis, R.C., J. Biol. Chem., 98, 11-16, 1932.

59) Hickee, E.L., Brink, N.G., Konlueny, F.R., Wood, T.R., Folkers, K., Science, 108, 134, 1948.

60) Bertrand, G., C. R. Acad. Sci. Paris, 124, 1032-1038, 1385-1388, 1897.

61) McHargue, J.S., Jour. Amer. Chem. Soc., 38, 2832-2836, 1914.

62) Samuel, G., Piper, C.S., J. Agric. S. Aust., 31, 896-705, 789-799, 1928.

63) Samuel, G., Piper, C.S., Ann. Appl. Biol., 16, 482-524, 1928.

64) Pettinger, N.A., Henderson, R.G., Wingard, A., Phytopathology, 32, 38-51, 1932.

65) Gallagher, P.H., Wallan, T., J. Agric. Sci., 33, 187-203, 1943.

66) McHargue, J.S., Lee, H.A., Phytopath., 18, 775-796, 1928.

67) Pethybridge, G.H., J. Minist. Agric., 43, 55-59, 1936.

68) Piper, C.S., J. Agric. Sci., 31, 448-453, 1941.

69) Harmer, P. M., Shaeman, O.D., Soil Sci. Soc. Amer. Proc., 8, 334-340, 1944.

70) McGarrison, R., Indian J. M. Rev., 14, 841-848, 1927.

71) McHargue, J.S., Am. J. Physiol., 77, 245-255, 1926.

72) Orent, E.R., McCollum, E.V., J. Biol. Chem., 92, 651-678, 1931.

73) Shils, Maurice E., McCollum, E.V., J. Nutr., 26, 1-19, 1943.

74) Wilgus, H.S., Norris, L.C., Heuser, G.F., J. Nutr., 14, 155-167, 1937.

75) Gallup, W.D., Norris, L.C., Science, 87, 18-19, 1938.

76) Caskey, C.D., Gallup, W.D., Norris, L.C., J. Nutr., 17, 407-417, 1939.

77) Barnes, L.L., Sperling, G., Maynard, L.A., Proc. Soc. Exper. Biol. & Med., 46, 562-565, 1941.

78) Miller, R.C., Keith, T.B., McCarthy, M.A., Thorp, W.T., Proc. Soc. Exper. Biol. & Med., 45, 50-51, 1940.

79) Kehoe, R.A. Cholak, J., Story, R.V., J. Nutr., 20, 85-98, 1940.

80) Finch, A.H., Kinnison, A.F., Tech. Bull. Arizona Agric. Exp. Sta., 47, 407-442, 1933.

81) Reed, H.S., Dufrenoy, J., Hilgardia, 9, 113-137, 1935.

82) Chandler, W.H., Hoagland, D.R., Hibbard, P.L., Proc. Amer. Soc. Hort. Sci., 28, 556-560, 1932.

83) Johnston, J.C., Calif. Citrograph, 18, 116-118, 1933.

84) Barnetts, R.M., Warner, J.D., Soil Sci., 39, 146-156, 1935.

85) Todd, W.R., Elvehjem, C.A., Hart, E.B., Am. J. Physiol., 107, 146-156, 1934.

86) Keilin, D., Mann, T., Biochem. J., 34, 1163, 1940.

87) Scott, D.A., Fisher, A.M., Biochem. J., 29, 1048-1054, 1935.

88) Vallee, B.L., Fluharty, R.G., J. Clin. Invest., 26, 1199, 1947.

89) Ter Meulen, H., Nature, 130, 966, 1932.

71) McHargue, J.S., Am. J. Physiol., 77, 245-255, 1926.

72) Grant, E.R., McCollum, E.V., J. Biol. Chem., 82, 851-879, 1931.

73) Shils, Maurice E., McCollum, E.V., J. Nutr., 26, 1-19, 1943.

74) Wilgus, H.S., Norris, L.C., Heuser, G.F., J. Nutr., 14, 155-167, 1937.

75) Gallup, W.D., Norris, L.C., Science, 87, 18-19, 1938.

76) Cheney, G.D., Gallup, W.D., Norris, L.C., J. Nutr., 17, 407-417, 1938.

77) Barnes, L.I., Sperling, O., Maynard, L.A., Proc. Soc. Exper. Biol. & Med., 48, 582-585, 1941.

78) Miller, R.C., Keith, T.S., McCarthy, M.A., Thorp, W.T., Proc. Soc. Exper. Biol. & Med., 45, 50-51, 1940.

79) Kehoe, R.A. Cholak, J., Story, H.V., J. Nutr., 20, 85-88, 1940.

80) Finch, A.H., Kinnison, A.F., Tech. Bull. Arizona Agric. Exp. Sta., 47, 407-443, 1933.

81) Read, H.S., Dufrenoy, J., Hilgardia, 9, 113-137, 1935.

82) Chandler, W.H., Hoagland, D.R., Hibbard, P.L., Proc. Amer. Soc. Hort. Sci., 28, 556-560, 1932.

83) Johnston, J.C., Calif. Citrograph, 18, 116-118, 1933.

84) Barnette, R.M., Warner, J.D., Soil Sci., 32, 146-156, 1935.

85) Todd, W.R., Elvehjem, C.A., Hart, E.B., Am. J. Physiol., 107, 146-156, 1934.

86) Kellin, D., Mann, T., Biochem. J., 34, 1165, 1940.

87) Scott, D.A., Fisher, A.M., Biochem. J., 29, 1048-1054, 1935.

88) Vallee, B.L., Flubarty, R.G., J. Clin. Invest., 26, 1199, 1947.

89) Ter Meulen, H., Nature, 130, 966, 1932.

90) Arnon, D.J., Stout, P.R., Plant Physiol., 14, 599-602, 1939.

91) Hoagland, D.R., Proc. Amer. Soc. Hort. Sci., 38, 8-12, 1940.

92) Piper, C.S., Jour. Aust. Inst. Agr. Sci., 6, 162-164, 1940.

93) Anderson, A.J., Jour. Aust. Inst. Agr. Sci., 8, 73-75, 1942.

94) Ferguson, W.S., Lewis, A.H., Watson, S.J., J. Agric. Sci., 33, 44-51, 1943.

95) Beeson, K.C., Soil Science, 60, 10, 1945.

90) Arnon, D.I., Stout, P.R., Plant Physiol., 14, 599–
602, 1939.

91) Hoagland, D.R., Proc. Amer. Soc. Hort. Sci., 38,
9–12, 1940.

92) Piper, C.S., Jour. Amst. Inst. Agr. Sci., 8, 182–
184, 1940.

93) Anderson, A.J., Jour. Amst. Inst. Agr. Sci., 2.
73–78, 1942.

94) Ferguson, W.S., Lewis, A.H., Watson, S.J., J. Agric.
Sci., 33, 44–51, 1943.

95) Beeson, K.C., Soil Science, 60, 10, 1945.

Ed.

Stored

Service Paper
1949
Vallee, N/N.

Vallee, N.N.
Epidemiology of
Fluorine, Iodine,
Manganese, Copper, Zinc
in Soils, plants, anim.
and minerals.

W Grants 1490

APR 5 1957

139 683

LAPOINTE JANICE A

Rm. Use

Ed.

Service Paper
1949
Vallee, N.N.
Stored